APPLICATION OF QUALITY BY DESIGN (QBD) IN DEVELOPING BIOEQUIVALENT ATORVASTATIN TABLETS

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Abbreviations

RLD	: Reference Listed Drug	No.	: Number
USP	: United State Pharmacopeia	BCS	: Biopharmaceutical Classification System
API	: Active Pharmaceutical Ingredient	LNB	: Laboratory Note Book
CMA	: Critical Material Attributes	RPM	: Revolution Per Minute
mm	: Millimeter	mg	: Milligram
min	: Minutes	sec	: Seconds
Ref.	: Reference	RSD	: Relative Standard Deviation
CQAs	: Critical Quality Attributes	AR	: Analytical Reference
CPPs	: Critical Process Parameters	NLT	: Not Less Than
QTPP	: Quality Target Product Profile	API	: Active Pharmaceutical Ingredients
kp	: Kilopond	CRC	: Child Resistant Closure
PK	: Pharmacokinetic	NMT	: Not More Than
CDER	: Center for Drug Evaluation and Research	ICH	: International Council for Harmonization
BRL	: Below Reporting Level	N/A	: Not Applicable
LOD	: Loss on drying	SD	: Standard Deviation
kg	: Kilogram	DOE	: Design of Experiment
C_{max}	: Maximum Plasma Concentration	AUC	: Area under the Curve
ANDA	: Abbreviated New Drug Application	T_{max}	: Time for achieving Maximum Plasma Concentration
BE	: Bioequivalence	CFR	: Code of Federal Regulations
QS	: Quantity Sufficient	BDL	: Below Detection Limit
RH	: Relative Humidity	cGMP	: Current Good Manufacturing Practice
NF	: National Formulary	AAP	: Atomizing Air Pressure
CV	: Coefficient of variation	mL	: Milliliter
CI	: Confidence Interval	Avg.	: Average
FT	: First time	LT	: Last Time
KF	: Karl fischer	IP-CQAs	: In-Process Critical Quality Attributes
CFM	: Cubic feet per minute	PSD	: Particle Size Distribution
ND	: Not Detected	DMF	: Drug Master File
Min.	: Minimum	Max.	: Maximum
Temp.	: Temperature	BMR	: Batch Manufacturing Record

Application of Quality by Design (QbD) in Developing Bioequivalent Atorvastatin Tablets

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1.1 Overview

The objective was to develop a generic version of approved Reference Listed Drug (RLD) product Lipitor® (Atorvastatin calcium) Tablets, 10 mg, 20 mg, 40 mg and 80 mg manufactured by UPJOHN MANUFACTURING IRELAND UNLTD (Formerly Pfizer Inc.) which will be manufacturable, chemically and physically stable throughout the manufacturing process and product shelf life, and bioequivalent.

The drug product development is outlined below:

- Analysis of the reference product.
- Quality Target Product Profile (QTPP)
- Critical Quality Attributes (CQAs) for the drug product
- Formulation development
- Formulation and process optimization
- Manufacture of scale up and exhibit batch
- Pivotal bio study
- Control strategy for commercial product manufacturing.

Initially, the quality target product profile was defined based on the properties of the Drug Substance, physicochemical characterization of the RLD product and consideration of the RLD label. Our investigation during pharmaceutical development was focused on those CQAs and physical attributes that could be impacted by a realistic change to the drug product formulation or manufacturing process. For generic Atorvastatin Calcium Tablets, CQAs included assay, content uniformity, dissolution and degradation products.

Due to low API content in dosage form and poorly flowing and compressibility nature, direct compression method is ruled out and preferred wet granulation method to improve the flow-ability and compressibility of the powder mixture. Both wet high-shear and fluidized-bed technique were utilized during initial formulation and process development but finally fluid bed granulation technique selected to get soft granules with better disintegration and dissolution profile compare to the high shear granulation. Based on scientific rationale and use of purified water in reference product as granulating solvent, same solvent was used for wet granulation process of generic Atorvastatin Calcium Tablets. Our ultimate target was to designing and developing formulations and manufacturing processes to ensure predefined product quality.

Finalization of the prototype formulation was performed throughout the formulation development studies based on the product performance study and stability requirements. Formulation optimization and process optimization studies were executed to identify the potential critical process parameters and quality attributes for each unit operation. Critical process parameters and quality attributes identified during process characterization for each unit operation were used to establish control strategy for commercial batch manufacturing.

Excipients were chosen based on the functionality of those in the reference product, literature information, and experience with similar manufacturing process. There are no novel excipients used in the drug product formulation.

Atorvastatin calcium is a biopharmaceutics Classification System (BCS) Class II compound shows low solubility across the physiological pH range and high permeability. The dissolution method recommended by OGD for this product was utilized for formulation and process development and same was adopted for QC release purpose.

Scale-up principles and plans were discussed for scaling up of lab batch to scale-up batch then to exhibit batch scale and proposed commercial scale batch size is up to and including a factor of 10 times the size of the exhibit batch. The operating ranges for identified critical process parameters (CPPs) at commercial scale is proposed and will be validated and continually verified during routine commercial manufacturing. Three exhibit batches of generic Atorvastatin calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg manufactured under cGMP with same formulation, same specifications, and at same site.

Bioequivalence studies performed for the Atorvastatin Calcium Tablets, 80 mg manufactured using the proposed commercial process and formulation, indicating equivalent in vivo performance to Lipitor® (Atorvastatin calcium) Tablets, 80 mg both at fasting and fed condition. The batch used in bioequivalence studies was also compared in vitro against Atorvastatin calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg indicate similar dissolution profiles.

1.2 Analysis of the Reference Listed Drug Products

1.2.1 Clinical Pharmacology

Atorvastatin calcium is a selective and competitive inhibitor of HMG-CoA reductase.

1.2.2 Pharmacokinetics

Absorption:

Atorvastatin calcium is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to Atorvastatin calcium dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether Atorvastatin calcium is given with or without food. Plasma Atorvastatin calcium concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.

Distribution:

Mean volume of distribution of Atorvastatin calcium is approximately 381 liters. Atorvastatin calcium is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, Atorvastatin calcium is likely to be secreted in human milk.

Metabolism:

Atorvastatin calcium is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. In vitro inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of Atorvastatin calcium. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. In vitro studies suggest the importance of Atorvastatin calcium metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of Atorvastatin calcium in humans following co-administration with erythromycin, a known inhibitor of this isozyme. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Elimination:

Atorvastatin calcium and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of Atorvastatin calcium in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of Atorvastatin calcium is recovered in urine following oral administration.

1.2.3 Indications and Usage

Atorvastatin calcium is an HMG-CoA reductase inhibitor indicated as an adjunct therapy to diet to:

- Reduce the risk of MI, stroke, revascularization procedures, and angina in adult patients without CHD, but with multiple risk factors.
- Reduce the risk of MI and stroke in adult patients with type 2 diabetes without CHD, but with multiple risk factors.
- Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in adult patients with CHD.
- Reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.
- Reduce elevated TG in adult patients with hypertriglyceridemia and primary dysbetalipoproteinemia.
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH).
- Reduce elevated total-C, LDL-C, and apo B levels in pediatric patients, 10 years to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) after failing an adequate study of diet therapy.

1.2.4 Physicochemical Characterization

The physicochemical characterization of the RLD is summarized in Table 1.

Table 1: Physicochemical Characterization of Lipitor® (Atorvastatin Calcium) Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Characterization	**Lipitor® (Atorvastatin Calcium) Tablet, 80 mg**		**Lipitor® (Atorvastatin Calcium) Tablet, 40 mg**	**Lipitor® (Atorvastatin Calcium) Tablet, 20 mg**	**Lipitor® (Atorvastatin Calcium) Tablet, 10 mg**
	Lot No. W37799	**Lot No. CA9137**	**Lot No. AM9624**	**Lot No. AP8066**	**Lot No. CN1813**
Distributed by	Park Devis Division of Pfizer INC.				
NDC code	0071-0158-23	0071-0158-23	0071-0157-23	0071-0156-23	0071-0155-23
Description	White Elliptical, Film coated, Unscored tablets coded with “PD158” on one side and “80” on other side	White Elliptical, Film coated, Unscored tablets coded with “PD158” on one side and “80” on other side	White Elliptical, Film coated, Unscored tablets coded with “PD157” on one side and “40” on other side	White Elliptical, Film coated, Unscored tablets coded with “PD156” on one side and “20” on other side	White Elliptical, Film coated, Unscored tablets coded with “PD155” on one side and “10” on other side
Label Claim	Each tablet contains Atorvastatin Calcium eq. to 80 mg Atorvastatin	Each tablet contains Atorvastatin Calcium eq. to 80 mg Atorvastatin	Each tablet contains Atorvastatin Calcium eq. to 40 mg Atorvastatin	Each tablet contains Atorvastatin Calcium eq. to 20 mg Atorvastatin	Each tablet contains Atorvastatin Calcium eq. to 10 mg Atorvastatin
Scoring Configuration	No score	No score	No score	No score	No score
Packaging Profile	White rectangular shape HDPE bottle with CR closure for 30’s count				
Storage condition	Lipitor ® tablets should be stored between 20 – 25°C (68 – 77°F)				
Average weight (mg)	1231.26	1239.14	610.93	307.56	154.88

Characterization	**Lipitor® (Atorvastatin Calcium) Tablet, 80 mg**		**Lipitor® (Atorvastatin Calcium) Tablet, 40 mg**	**Lipitor® (Atorvastatin Calcium) Tablet, 20 mg**	**Lipitor® (Atorvastatin Calcium) Tablet, 10 mg**
	Lot No. W37799	**Lot No. CA9137**	**Lot No. AM9624**	**Lot No. AP8066**	**Lot No. CN1813**
Length (mm)	-	19.14	15.32	12.04	9.58
Width (mm)	-	10.14	7.93	6.20	4.95
Thickness (mm)	-	7.47	5.80	4.49	3.47
Hardness (Kp)	-	26.10	19.03	15.60	8.15
Disintegration without disc	-	FT- 04 min 10 sec LT- 04 min 21 sec	FT- 02 min 58 sec LT- 03 min 08 sec	FT- 02 min 01 sec LT- 02 min 08 sec	FT- 01 min 45 sec LT- 01 min 50 sec
pH	-	10.24	10.34	10.36	10.12
Expiry Date	Aug, 2020	Feb 28, 2022	Jul 31, 2021	Dec 31, 2021	May 31, 2022
Assay by HPLC	101.4%	100.3%	98.4%	97.7%	98.6%
Dissolution in USP Apparatus II (Paddle), Medium: Phosphate Buffer, pH 6.8; 900 mL, 75 RPM, (37.0 ± 0.5) °C, Time point: 30 min	Avg: 104 % Min: 102% Max:106%	Avg: 100% Min: 98% Max:102%	Avg:95% Min: 93% Max:95%	Avg:94% Min: 92% Max:98%	Avg:92% Min: 88% Max:100%
Water content by KF	2.5% w/w	3.8% w/w	4.2% w/w	3.5% w/w	4.3% w/w
Organic Impurities by HPLC					
Atorvastatin pyrrolidone analog	0.05%	0.06%	0.05%	0.03%	0.05%
Atorvastatin related compound H	0.02 %	0.03%	0.02%	0.03%	0.04%

Characterization	**Lipitor® (Atorvastatin Calcium) Tablet, 80 mg**		**Lipitor® (Atorvastatin Calcium) Tablet, 40 mg**	**Lipitor® (Atorvastatin Calcium) Tablet, 20 mg**	**Lipitor® (Atorvastatin Calcium) Tablet, 10 mg**
	Lot No. W37799	**Lot No. CA9137**	**Lot No. AM9624**	**Lot No. AP8066**	**Lot No. CN1813**
Atorvastatin epoxypyrrolooxazin 6-hydroxy analog	0.11%	Not Detected	Not Detected	Not Detected	Not Detected
Atorvastatin epoxypyrrolooxazin 7-hydroxy analog	Not Detected	Not Detected	0.06%	0.03%	Not Detected
Atorvastatin epoxy THF analog & Atorvastatin related Compound D	0.07%	0.08%	0.12%	0.09%	0.09%
Any other unspecified degradation product	0.07%	0.06%	0.10%	0.08%	0.10%
Total impurities	0.35%	0.33%	0.48%	0.36%	0.39%
Ref. AR No.	**DB0132**	**203793**	**203794**	**203795**	**203796**

1.2.5 Composition

Based on the RLD labeling, composition of Lipitor® (Atorvastatin Calcium) Tablets, 10 mg, 20 mg, 40 mg and 80 mg are listed in Table 2. The excipient function is assumed based on excipient category, literature data and prior experience with similar products.

Table 2: Composition of Reference Product Lipitor® (Atorvastatin Calcium) Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Component	Probable Function
Atorvastatin Calcium Trihydrate	API
Calcium carbonate	Basic diluent and to maintain alkaline pH in dosage form
Croscarmellose sodium	Disintegrant
Polysorbate 80	Surfactant/Solubilizer
Hydroxypropyl cellulose	Binder
Microcrystalline cellulose	Diluent
Lactose monohydrate	Diluent
Magnesium Stearate	Lubricant
Coating part	
Candelilla wax	Glazing & layering agent
Opadry white YS-1-7040	Coating agent
Simethicone emulsion	Antifoaming agent

1.3 Quality Target Product Profile (QTPP) for the ANDA Product

The QTPP forms the basis of design for the development of the drug product. The QTPP could include critical and non-critical elements. A sub-set of the QTPP is the Critical Quality Attributes (CQAs) which form the basis for the product specification.

Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) play an important role in achieving Critical Quality Attributes (CQAs) effectively. Based on RLD characterization and information gathered from RLD's approved label, a QTPP was defined to guide the development of a generic Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg that must be therapeutically equivalent to the RLD. Table 3 shows the QTPP for proposed generic drug product Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg.

Table 3. Quality Target Product Profile of the Generic Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg

QTPP Elements		**Target**	**Justification**
Dosage form		Tablet	Pharmaceutical equivalence requirement: same dosage form
Dosage design		Immediate release tablet without a score	Immediate release design needed to meet label claims
Route of administration		Oral	Pharmaceutical equivalence requirement: same route of administration
Dosage strength		Eq. base 80 mg, Eq. base 40 mg, Eq. base 20 mg & Eq. base 10 mg	Pharmaceutical equivalence requirement: same strengths
Pharmacokinetics		Immediate release enabling Tmax and AUC equivalent to RLD	Bioequivalence requirement Needed to ensure rapid onset and efficacy
Stability		Equivalent to RLD	Needed for commercialization
Drug product quality attributes	Physical Attributes	Pharmaceutical equivalence requirement: Must meet the same compendia or other applicable (quality) standards (i.e., identity, assay, purity, and quality).	
	Identification		
	Assay		
	Content Uniformity		
	Dissolution		
	Degradation Products		
	Water Content		
	Microbial Limits		
Container closure system	Container closure system qualified as suitable for this drug product	Needed to achieve the target shelf-life and to ensure tablet integrity during shipping	
Alternative methods of administration	None	None are listed in the RLD label.	

Table 4 summarizes the quality attributes of generic Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg and indicates which attributes are classified as drug product Critical Quality Attributes (CQAs). For this product, assay, content uniformity, dissolution and degradation products are identified as the subset of CQAs that have the potential to be impacted by the formulation and/or process variables and, therefore, will be investigated and discussed in detail in subsequent formulation and process development studies.

On the other hand, CQAs including identity, residual solvents, elemental impurities and microbial limits which are unlikely to be impacted by formulation and/or process variables will not be discussed in detail in the pharmaceutical development report. However, these CQAs are still target elements of the QTPP and are ensured through a good pharmaceutical quality system and the control strategy.

Table 4: Critical Quality Attributes (CQAs) of Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg

Quality Attributes of the Drug Product		**Target**	**Is this a CQA?**	**Justification**
Physical Attributes	Appearance	Acceptable color and shape to the patient. No visual tablet defects observed.	No	Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability.
	Odor	No unpleasant odor	No	In general, a noticeable odor is not directly linked to safety and efficacy, but odor can affect patient acceptability. For this product, neither the Drug substance nor the excipients have an unpleasant odor. No organic solvents will be used in the drug product manufacturing process.
	Size	Similar to RLD	No	For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the target for tablet dimensions is set similar to the RLD.
	Score configuration	Unscored	No	The RLD is an unscored tablet; therefore, the generic tablet will be unscored. Score configuration is not critical for the Atorvastatin Calcium Tablets.
Identification		Positive for Atorvastatin Calcium	Yes*	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity. Therefore, this CQA will not be discussed during formulation and process development.
Assay		100% w/w of Label claim	Yes	Assay variability will affect safety and efficacy. Process variables may affect the assay of the drug product. Thus, assay will be evaluated throughout product and process development.
Content uniformity		Conforms to USP <905>	Yes	Variability in content uniformity will affect safety and efficacy. Both formulation and process variables impact content uniformity, so this CQA will be evaluated throughout product and process development.

Quality Attributes of the Drug Product	Target	Is this a CQA?	Justification
Dissolution	NLT 80% (Q) at 30 minutes in 900 mL of pH 6.8 phosphate buffer using USP Apparatus II (Paddle) at 75 RPM	Yes	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile. This CQA will be investigated throughout formulation and process development.
Degradation Products	Atorvastatin pyrrolidone analog: NMT 0.5 % Atorvastatin related compound H: NMT 1.0 % Atorvastatin epoxypyrrolooxazin 6-hydroxy analog: NMT 0.5 % Atorvastatin epoxypyrrolooxazin 7-hydroxy analog: NMT 0.5 % Atorvastatin epoxy THF analog & Atorvastatin related Compound D: NMT 1.5% Any other unspecified degradation product: NMT 0.2% Total impurities: NMT 4.0%	Yes	Degradation products can impact safety and must be controlled based on ICH requirements or RLD characterization to limit patient exposure. The target for degradation products is set according to ICH requirements. Formulation and process variables can impact degradation products. Therefore, degradation products will be assessed during product and process development.
Residual Solvents	USP <467> option 1	Yes*	Residual solvents can impact safety. However, no solvent is used in the drug product manufacturing process and the drug product complies with USP <467> Option 1. Therefore, formulation and process variables are unlikely to impact this CQA.
Elemental Impurities	Comply with USP <232> and ICH Q3D requirements.	Yes*	None of the elements listed in the USP general chapter <232> and ICH Q3D is intentionally added in the manufacturing process, and based on the risk assessment / evaluation, none of the elements is more than the allowable limits as per USP < 232> and ICH Q3D. Therefore, formulation and process variables are unlikely to impact this CQA

Quality Attributes of the Drug Product	**Target**	**Is this a CQA?**	**Justification**
Water Content by KF	Not more than 6.0% w/w	No	Generally, water content may affect degradation and microbial growth of the drug product and can be a potential CQA. Water content limit determined based on input moisture content of API (in trihydrate form of atorvastatin calcium contains 3.5%-5.5% water), excipients combined with the API to manufacture a final dosage form and residual moisture in manufacturing process. Hence, moisture limit in this range will not impact stability.
Microbial Limits	Meets relevant pharmacopoeia criteria	Yes*	Non-compliance with microbial limits will impact patient safety. However, in this case, the risk of microbial growth is very low because granules will dry at high temperature. Therefore, this CQA will not be discussed in detail during formulation and process development

* Formulation and process variables are unlikely to Impact the CQA. Therefore, the CQA will not be investigated and discussed in detail in subsequent risk assessment and pharmaceutical development. However, the CQA remains a target element of the drug product profile and should be addressed accordingly.

1.4 Dissolution Method Development

Atorvastatin Calcium is a BCS Class II compound shows low solubility across the physiological pH range and high permeability. The dissolution method recommended by OGD (900 mL of pH 6.8 phosphate buffer using USP Apparatus II at 75 RPM, 37 ℃) was utilized for formulation and process development and same was adopted for QC release purpose. The dissolution tolerance NLT 80% (Q) in 30 min set based on the product development data.

From pH solubility profile, highest solubility found at pH 6.8 and lowest solubility observed at 0.1 N HCl (≈ pH 1.25) and acetate buffer pH (pH 4.50). Moreover, degradation of the atorvastatin calcium noticed at acidic condition due to formation of Lactone impurity (Atorvastatin Calcium RC H) at acidic condition. Hence, pH 6.8 phosphate buffer considered suitable dissolution testing of Atorvastatin Calcium tablets.

2.0 Components of Drug Product

2.1 APIs

2.1.1 Physicochemical and Biological Properties of API

Appearance: Atorvastatin Calcium is white to off white crystalline powder.

pKa: pKa 4.46

pH: 6. 48 to 6.53

Melting Point: About 169 °C

Polymorphism:

As per literature Atorvastatin calcium exhibits polymorphism and reference product marketed from the designated crystalline form I which is the most stable form. The 2θ values in XRD studies indicated that atorvastatin calcium manufactured by Arch Pharmalabs Ltd were comparable with standard values given in the patent WO 9703959, which confirms the Form-I of the drug substance and similarity with polymorphic form used in reference listed products.

Flow Properties of Drug Substance:

Atorvastatin calcium micronized powder exhibits very poor flow properties and shows adhere ability on the manufacturing/processing equipment.

Chemical Stability in Solid State and in solution of Drug substance (Transcribed from DMF):

Table 5: Force Degradation Study of Atorvastatin Calcium Trihydrate USP

Stress	**Conditions**	**% Degradation**
Acid Hydrolysis	0.1M HCl, 95°C for up to 30.0 min	26.87
Acid Hydrolysis	1M HCl, 95°C for up to 30.0 min	27.79
Acid Hydrolysis	0.1M HCl, At room temperature for up to 30.0 min	2.7
Base Hydrolysis	0.1M NaOH, 95°C for up to 30.0 min	0.17
Base Hydrolysis	1M NaOH, 95°C for up to 30.0 min	0.21
Heat and water	In water 95°C for up to 30.0 min	2.15

Inference:

From the results it is evident that molecule is unstable at acid and no significant degradation occurred in basic conditions.

Photostability of atorvastatin calcium USP:

Photostability of drug substance conducted with the aim to evaluate the overall photosensitivity (impurities generation) of the material for method development purposes and/or packaging material selection for drug product. Samples are exposed to ensure 1.2 million Lux hr.; 200 watt hr/Sq meter and results (Organic impurities) of controlled and exposed samples presented at Table 6.

Table 6: Photostability of Atorvastatin Calcium USP

Tests/Specifications	Controlled	Exposed
Organic Impurities by HPLC		
Atorvastatin Related Compound A	0.03 %	0.04 %
Atorvastatin Related Compound B	ND	ND
Atorvastatin Related Compound C	ND	ND
Atorvastatin Related Compound D	0.00 %	0.01 %
Any other Known impurity	0.02 %	0.02 %
Any other Unknown impurity	0.09 %	0.10 %
Total impurities (Not including Atorvastatin Related Compound E)	0.27 %	0.30 %

Inference:

From the above it can be inferred that UV light has no significant effect to accelerate the impurity generation of Atorvastatin calcium.

Biopharmaceutics Classification:

Atorvastatin Calcium USP is considered a Class II compound (Low solubility/High permeability).

Aqueous Solubility as a Function of pH:

The solubility of Atorvastatin Calcium Trihydrate USP in aqueous media as a function of pH was measured immediately after dissolution and is presented in Table 7.

Table 7: pH Solubility Profile of Atorvastatin Calcium Trihydrate USP

S/N	Media	Final pH	Solubility (mg/mL)
1.	pH 1.2 Hydrochloric Acid medium	1.25	0.02
2.	pH 1.4 Hydrochloric Acid medium	1.46	0.02
3.	pH 4.5 Acetate Buffer USP	4.50	0.05
4.	pH 5.5 Phosphate Buffer USP	5.54	0.12
5.	pH 6.0 Phosphate Buffer USP	6.03	0.15
6.	pH 6.8 Phosphate Buffer USP	6.83	0.19
7.	Purified Water	7.30	0.14

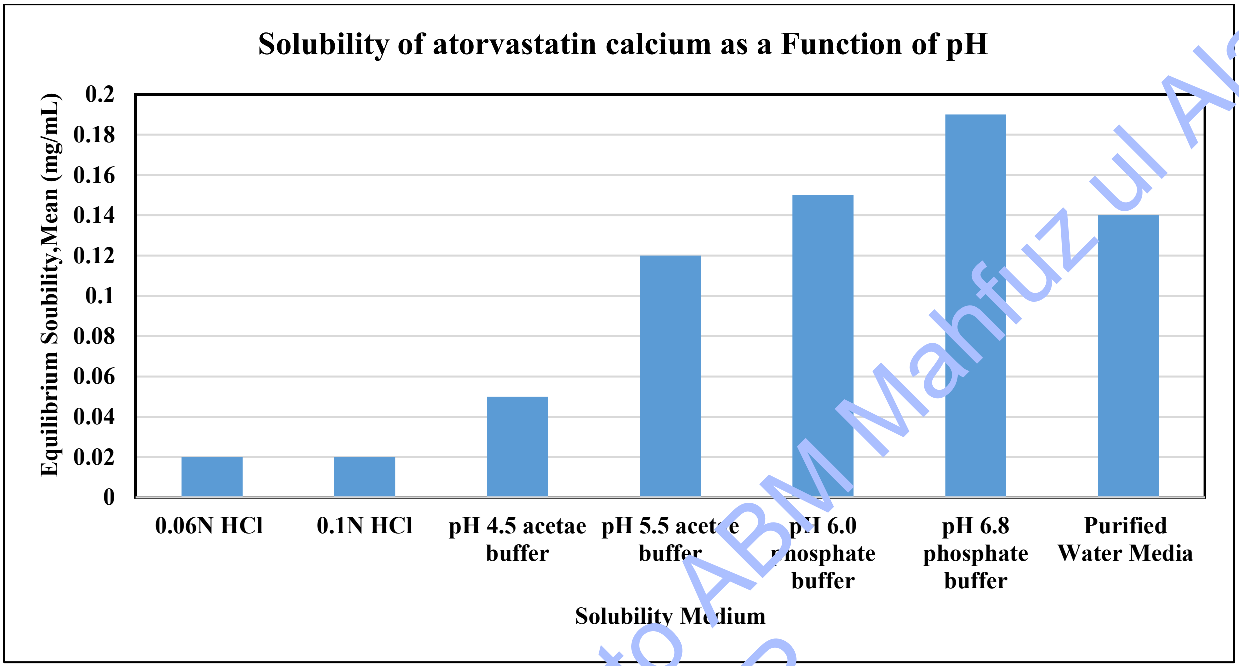

Figure 1: Solubility of Atorvastatin Calcium USP as a Function of pH

On the basis the above solubility data of Atorvastatin Calcium USP, it is showed that solubility of the atorvastatin calcium is pH dependent and solubility increases with increase in pH. Lowest solubility found at acidic medium and highest solubility found at pH 6.8.

The highest immediate release dose strength developed for Atorvastatin Calcium is 80 mg. The volume of aqueous media required to dissolve 80 mg of Atorvastatin Calcium at the highest solubility is 421 mL. A drug substance is considered highly soluble when the highest strength is soluble in 250 mL or less of aqueous media over the pH range of 1-6.8 Therefore, Atorvastatin Calcium is considered a low solubility drug.

2.1.2 Risk Assessment of Drug Substance Attributes

Risk assessment of the Drug Substance attributes was performed to evaluate the impact that each attribute could have on the drug product CQAs. The outcome of the assessment and the accompanying justification is provided as a summary in the pharmaceutical development report. The relative risk that each attribute presents was ranked as high, medium or low. The high risk attributes warranted further investigation whereas the low risk attributes required no further investigation. The medium risk is considered acceptable based on current knowledge. Further investigation for medium risk may be needed in order to reduce the risk. The same relative risk ranking system was used throughout pharmaceutical development and is summarized in Table 8.

Table 8: Overview of Relative Risk Ranking System

Low	Broadly acceptable risk. No further investigation is needed
Medium	Risk is acceptable. Further investigation may be needed in order to reduce the risk
High	Risk is unacceptable. Further investigation is needed to reduce the risk

Based upon the physicochemical and biological properties of the drug substance, the initial risk assessment of drug substance attributes on drug product CQAs as well as on intermediate CQAs along with justification is shown in Table 9 and Table 10.

Table 9: Initial Risk Assessment of the Drug Substance Attributes

Drug product CQAs	**Drug Substance (API) Attributes**								
	Solid State Form	**Particle Size Distribution**	**Hygroscopicity**	**Solubility**	**Water Content**	**Residual Solvents**	**Process Impurities**	**Chemical Stability**	**Flow Properties**
Assay	Low	Medium	Low	Low	Low	Low	Low	High	High
Content uniformity	Low	High	Low	Low	Low	Low	Low	Low	High
Dissolution	Medium	High	Low	High	Low	Low	Low	Low	Low
Degradation Products	Medium	Low	Low	Low	Medium	Medium	Medium	High	Low

Table 10: Justification for the Initial Risk Assessment of the drug substance attributes

API Attributes	**Drug Products CQAs**	**Risk Category**	**Justification**
Solid State Form	Assay	Low	API solid state form does not affect tablet assay and content uniformity. The risk is **Low.**
	Content uniformity	Low	
	Dissolution	Medium	Crystalline and amorphous forms have different properties due to the unique arrangement of molecules in the crystal lattice varying density of packing, and/or by varying hydrogen-bond network Drug substance with different polymorphic forms may have different chemical stability as well as solubility and may impact the degradation products and dissolution of the tablet. As per literature, atorvastatin calcium exhibits polymorphism and reference product marketed from the designated crystalline form 1 which is the most stable form. Same polymorphic form as of reference product (crystalline form 1) considered for development of generic atorvastatin calcium tablets. Hence, the risk is **medium.**
	Degradation Products	Medium	
Particle Size Distribution (PSD)	Assay	Medium	Particle size distribution may adversely impact uniformity of the drug at granulation stage which can impact the uniformity of the dosage unit for this low API content drug product and in extreme cases, may cause an assay failure. The risk is **medium** for assay and **high** for Content uniformity**.**
	Content uniformity	High	
	Dissolution	High	The drug substance is a BCS class II compound; therefore, PSD can affect dissolution. The risk is **High.**
	Degradation Products	Low	Generally, PSD is unlikely to impact degradation products. The risk is **Low.**
Hygroscopicity	Assay	Low	Atorvastatin Calcium is non-hygroscopic. The risk is **Low.**
	Content uniformity	Low	
	Dissolution	Low	
	Degradation Products	Low	

API Attributes	**Drug Products CQAs**	**Risk Category**	**Justification**
Solubility	Assay	Low	Solubility does not affect tablet assay, content uniformity and degradation products. The risk is **Low.**
	Content uniformity	Low	
	Degradation Products	Low	
	Dissolution	High	The drug substance is a BCS class II compound, hence, solubility of molecule can impact dissolution. The risk is **High.**
Water Content	Assay	Low	Moisture content is unlikely to impact assay, content uniformity and dissolution. The risk is **Low.**
	Content uniformity	Low	
	Dissolution	Low	
	Degradation Products	Medium	Water content (3.5-5.5%, w/w) present in the trihydrate form of atorvastatin calcium and this content generally will not impact the dosage form stability. Therefore, the risk is **Medium.**
Residual Solvent	Assay	Low	Residual solvents are controlled in the API specification and comply with USP <467> option 1. The risk is **Low.**
	Content uniformity	Low	
	Dissolution	Low	
	Degradation Products	Medium	Residual solvent can impact on degradation products. However, residual solvents are controlled in the API as per USP <467>. Therefore, the risk is **Medium.**
Process impurities	Assay	Low	Process impurities are unlikely to impact assay, content uniformity and dissolution. The risk is **Low.**
	Content uniformity	Low	
	Dissolution	Low	
	Degradation Products	Medium	Process impurities can impact on degradation products Impurity limits comply with ICH Q3A recommendations. Within this range, process impurities are unlikely to impact on degradation products. The risk is **Medium.**

API Attributes	Drug Products CQAs	Risk Category	Justification
Chemical Stability	Assay	High	Atorvastatin is susceptible to auto oxidation and acidic degradation. Therefore, chemical stability may affect drug product assay and degradation products. The risk is **High.**
	Degradation Products	High	
	Content uniformity	Low	Tablet content uniformity is unrelated to API chemical stability. The risk is **Low.**
	Dissolution	Low	Tablet dissolution is mainly impacted by API solubility and particle size distribution. Tablet dissolution is unrelated to API chemical stability. The risk is **Low.**
Flow Properties	Assay	High	Atorvastatin calcium has very poor flow properties which may influence uniformity of drug distribution at granulation stage and ultimately on assay and content uniformity. As the concentration of API in drug product is around 7.3% w/w, that's why the risk is **High**.
	Content uniformity	High	
	Dissolution	Low	The flow ability of the API is not related to its degradation pathway or dissolution. The risk is **Low.**
	Degradation Products	Low	

2.1.3 Excipients

The excipients used in generic Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg were chosen based on the functionality of those in the reference product, literature information, and experience with similar manufacturing process.

2.1.3.1 Excipient Compatibility Studies

Excipient-API compatibility was performed in ratio expected in the final formulation. Table 12, Table 13 and Table 14 summarizes the chemical characterization results of compatibility studies.

Table 11: Physical Characterization of Excipient Compatibility Studies

Sample Name	**Sample ID**	**Initial**	**14 days Analysis** **Condition : 40 ± 2°C and 75 ± 5% RH (Open)**	**14 days Analysis** **Condition : 60 ± 2°C (Close)**	**28 Days Analysis** **Condition : 40 ± 2°C and 75 ± 5% RH (Open)**	**28 Days Analysis** **Condition : 60 ± 2°C (Close)**
Atorvastatin calcium USP	CS-A001-01	White to off-white crystalline powder	White to off-white granular powder	White to off-white granular powder	White to off-white granular powder	White to off-white granular powder
Atorvastatin calcium USP+ Microcrystalline cellulose	CS-A001-14	White powder	White powder	White powder	White powder	White powder
Atorvastatin calcium USP+ Lactose monohydrate	CS-A001-15	Off white powder	Brown color powder	Brown color powder	Brown color powder	Brown color powder
Atorvastatin calcium USP+ Sodium starch glycolate	CS-A001-16	White powder	White powder	White powder	White powder	White powder
Atorvastatin calcium USP+ Croscarmellose sodium	CS-A001-17	White free flowing powder	White free flowing powder	White free flowing powder	White free flowing powder	White free flowing powder
Atorvastatin calcium USP+ Hydroxypropyl cellulose	CS-A001-18	Cream color powder	Brown color sticky powder	Cream color powder	Brown color sticky powder	Cream color powder
Atorvastatin calcium USP+ Precipitated calcium carbonate	CS-A001-19	White powder	White powder	White powder	White powder	White powder
Atorvastatin calcium USP+ Magnesium stearate	CS-A001-20	Almost white powder	Almost white powder	Almost white powder	Almost white powder	Almost white powder
Atorvastatin calcium USP+ Polysorbate 80	CS-A001-21	Brown color powder	Brown color sticky colloidal structure	Brown color sticky colloidal structure	Brown color sticky colloidal structure	Brown color sticky colloidal structure
Atorvastatin calcium USP+ Opadry clear (YS-1R 7006)	CS-A001-22	White powder	White powder	White powder	White powder	White powder
Atorvastatin calcium USP+ Opadry II white (85F18422)	CS-A001-23	White powder	White powder	White powder	White powder	White powder
Atorvastatin calcium USP+ Hypromellose 2910, 6 cps	CS-A001-24	Off-white powder	Yellowish color; lump formation; on shaking remain same	Off-white powder	Yellowish color; lump formation; on shaking remain same	Off-white powder
Atorvastatin calcium USP+ All Excipient (expected ratio in formulation)	CS-A001-25	White granule powder	Brown color granular powder	Brown color granular powder	Brown color granular powder	Brown color granular powder

Sample Name	Sample ID	Initial	14 days Analysis Condition : 40 ± 2°C and 75 ± 5% RH (Open)	14 days Analysis Condition : 60 ± 2°C (Close)	28 Days Analysis Condition : 40 ± 2°C and 75 ± 5% RH (Open)	28 Days Analysis Condition : 60 ± 2°C (Close)
Atorvastatin calcium USP+ Microcrystalline cellulose+ Precipitated calcium carbonate	CS-A001-26	White cream color powder	Off-white granular powder	Off-white granular powder	Off-white granular powder	Off-white granular powder
Atorvastatin calcium USP+ Lactose monohydrate + Precipitated calcium carbonate	CS-A001-27	White to off-white granular powder	White to off-white granular powder	White to off-white granular powder	White to off-white granular powder	White to off-white granular powder
Atorvastatin calcium USP+ Sodium starch glycolate+ Precipitated calcium carbonate	CS-A001-28	White powder	White powder	White powder	White powder	White powder
Atorvastatin calcium USP+ Croscarmellose sodium+ Precipitated calcium carbonate	CS-A001-29	Off-white powder	Off-white powder	Off-white powder	Off-white powder	Off-white powder
Atorvastatin calcium USP+ Polysorbate 80 + Precipitated calcium carbonate	CS-A001-30	One portion white powder and another portion Brown color powder	One portion white powder and another portion Brown color sticky colloidal structure	One portion white powder and another portion Brown color sticky colloidal structure	One portion white powder and another portion Brown color sticky colloidal structure	One portion white powder and another portion Brown color sticky colloidal structure

Table 12: Chemical Characterization (pH and water content) of Excipient Compatibility Studies

Sample Name	Sample ID	Initial		14 days Analysis		14 days Analysis		28 Days Analysis		28 Days Analysis	
				Condition : 40 ± 2°C and 75 ± 5% RH (Open)		Condition : 60 ± 2°C (Close)		Condition : 40 ± 2°C (Open)		Condition : 60 ± 2°C (Close)	
		pH	Water Content	pH	Water Content	pH	Water Content	pH	Water Content	pH	Water Content
Atorvastatin Calcium USP	CS-A001-01	6.90	4.66	6.15	4.85	6.71	4.40	7.21	4.63	9.90	4.67
Atorvastatin calcium USP+ Microcrystalline cellulose	CS-A001-14	6.05	5.33	6.36	5.08	6.37	4.94	6.54	5.63	6.98	5.02
Atorvastatin calcium USP+ Lactose monohydrate	CS-A001-15	6.13	5.02	6.86	2.53	6.38	5.06	6.85	5.00	6.31	5.09

Sample Name	Sample ID	Initial		14 days Analysis		14 days Analysis		28 Days Analysis		28 Days Analysis	
				Condition : 40 ± 2°C and 75 ± 5% RH (Open)		Condition : 60 ± 2°C (Close)		Condition : 40 ± 2°C (Open)		Condition : 60 ± 2°C (Close)	
		pH	Water Content	pH	Water Content	pH	Water Content	pH	Water Content	pH	Water Content
Atorvastatin calcium USP+ Sodium starch glycolate	CS-A001-16	6.86	4.56	6.94	4.63	7.04	4.43	9.09	5.45	6.99	4.62
Atorvastatin calcium USP+ Croscarmellose sodium	CS-A001-17	6.36	2.98	6.37	0.00	6.22	3.95	7.19	5.67	6.37	3.69
Atorvastatin calcium USP+ Hydroxypropyl cellulose	CS-A001-18	6.46	4.04	6.26	1.73	6.61	1.75	6.33	5.41	6.53	4.47
Atorvastatin calcium USP+ Precipitated calcium carbonate	CS-A001-19	9.87	0.96	9.48	1.01	7.37	1.25	9.80	0.94	9.82	1.11
Atorvastatin calcium USP+ Magnesium stearate	CS-A001-20	9.02	4.88	9.62	5.45	9.67	5.16	9.67	5.51	8.88	5.13
Atorvastatin calcium USP+ Polysorbate 80	CS-A001-21	6.99	4.50	6.60	3.37	6.76	0.72	7.54	3.30	7.54	0.79
Atorvastatin calcium USP+ Opadry clear (YS-1R-7006)	CS-A001-22	6.54	4.40	6.85	4.51	6.46	3.85	6.52	4.57	6.39	4.05
Atorvastatin calcium USP+ Opadry II white (85F18422)	CS-A001-23	6.46	3.47	5.16	3.67	6.47	2.66	6.97	3.82	6.39	2.92
Atorvastatin calcium USP+ Hypromellose 2910, 6 cps	CS-A001-24	6.60	4.39	7.33	5.09	6.91	4.46	7.65	5.36	6.60	4.09
Atorvastatin calcium USP+ All Excipient (expected ratio in formulation)	CS-A001-25	10.15	5.19	6.92	3.94	9.90	3.59	9.98	4.17	9.86	4.89
Atorvastatin calcium USP+ Microcrystalline cellulose+ Precipitated calcium carbonate	CS-A001-26	9.83	3.79	9.78	2.40	10.07	2.75	9.80	3.21	9.83	2.72
Atorvastatin calcium USP+ Lactose monohydrate + Precipitated calcium carbonate	CS-A001-27	9.72	3.65	9.78	2.36	9.83	3.33	9.74	2.65	9.77	2.90
Atorvastatin calcium USP+ Sodium starch glycolate+ Precipitated calcium carbonate	CS-A001-28	10.32	1.77	9.99	1.73	10.57	4.10	10.34	2.14	10.19	1.21
Atorvastatin calcium USP+ Croscarmellose sodium+ Precipitated calcium carbonate	CS-A001-29	9.93	1.98	9.80	2.15	9.83	1.09	10.19	2.35	10.02	1.15
Atorvastatin calcium USP+ Polysorbate 80 + Precipitated calcium carbonate	CS-A001-30	9.77	1.36	10.18	1.15	9.92	1.60	10.24	1.97	10.75	1.41

Table 13: Chemical Characterization (Organic impurities of Initial & 14 days) of Excipient Compatibility Studies

Sample Name	**Sample ID**	**Initial**					**14 days Analysis**					**14 days Analysis**				
		Impurity (%)					**Condition: 40 ± 2°C (Open)**					**Condition: 60 ± 2°C (Close)**				
							Impurity (%)					**Impurity (%**				
		Pyrrolidone analog	ATV RC H	ATVTHF analog + RC D	Max Ind. Imp	Total impurity	Pyrrolidone analog	ATV RC H	ATV THF analog + RC D	Max Ind. Imp	Total impurity	Pyrrolidone analog	ATV RC H	ATVTHF analog + RC D	Max Ind. Imp	Total impurity
Atorvastatin calcium USP	CS-A001-01	ND	0.03	0.02	0.06	0.31	0.05	0.05	0.02	0.02	0.23	0.04	0.04	0.01	0.02	0.20
Atorvastatin calcium USP+ Microcrystalline cellulose	CS-A001-14	0.05	0.04	0.02	0.01	0.18	0.05	0.07	0.02	0.02	0.24	0.05	0.02	0.01	0.03	0.20
Atorvastatin calcium USP+ Lactose monohydrate	CS-A001-15	0.05	0.04	0.02	0.01	0.17	0.05	0.21	0.02	0.02	0.41	0.06	0.08	0.02	0.02	0.26
Atorvastatin calcium USP+ Sodium starch glycolate	CS-A001-16	ND	0.04	0.02	0.01	0.12	0.05	0.17	0.02	0.04	0.38	0.05	0.07	0.02	0.02	0.24
Atorvastatin calcium USP+ Croscarmellose sodium	CS-A001-17	ND	0.03	0.03	0.01	0.14	0.04	0.13	0.02	0.03	0.30	0.04	0.05	0.01	0.02	0.22
Atorvastatin calcium USP+ Hydroxypropyl cellulose	CS-A001-18	0.04	0.04	0.02	0.01	0.15	0.05	0.08	0.02	0.03	0.28	0.05	0.03	0.01	0.03	0.18
Atorvastatin calcium USP+ Precipitated calcium carbonate	CS-A001-19	0.04	0.03	0.02	0.01	0.15	0.05	0.04	0.01	0.03	0.21	0.05	0.04	0.02	0.02	0.23

Sample Name	**Sample ID**	**Initial**					**14 days Analysis**					**14 days Analysis**				
		Impurity (%)					**Condition: 40 ± 2°C (Open)**					**Condition: 60 ± 2°C (Close)**				
							Impurity (%)					**Impurity (%**				
		Pyrrolidone analog	ATV RC H	ATVTHF analog + RC D	Max Ind. Imp	Total impurity	Pyrrolidone analog	ATV RC H	ATVTHF analog + RC D	Max Ind. Imp	Total impurity	Pyrrolidone analog	ATV RC H	ATVTHF analog + RC D	Max Ind. Imp	Total impurity
Atorvastatin calcium USP+ Magnesium stearate	CS-A001-20	0.04	0.04	0.02	0.01	0.15	0.07	0.22	0.02	0.03	0.40	0.06	0.08	0.02	0.02	0.24
Atorvastatin calcium USP+ Polysorbate 80	CS-A001-21	0.04	0.04	0.02	0.01	0.20	0.69	0.65	0.13	0.28	2.44	0.57	0.56	0.25	0.13	2.09
Atorvastatin calcium USP+ Opadry clear (YS-1R-7006)	CS-A001-22	0.04	0.04	0.02	0.01	0.16	0.11	[illegible]	0.03	0.04	0.46	0.14	0.23	0.05	0.03	0.58
Atorvastatin calcium USP+ Opadry II white (85F18422)	CS-A001-23	0.04	0.04	0.02	0.01	0.16	0.10	0.07	0.02	0.05	0.50	0.13	0.20	0.04	0.03	0.56
Atorvastatin calcium USP+ Hypromellose 2910, 6 cps	CS-A001-24	0.04	0.04	0.02	0.01	0.16	0.05	0.06	0.02	0.02	0.21	0.05	0.04	0.02	0.02	0.19
Atorvastatin calcium USP+ All Excipient (expected ratio in formulation)	CS-A001-25	0.04	0.04	0.02	0.01	0.15	ND	ND	0.02	ND	0.02	ND	ND	0.01	ND	0.01
Atorvastatin calcium USP+ Microcrystalline cellulose+	CS-A001-26	0.04	0.04	0.02	0.01	0.15	ND	ND	0.02	ND	0.02	ND	ND	0.02	ND	0.02

Sample Name	Sample ID	Initial					14 days Analysis					14 days Analysis				
							Condition: 40 ± 2°C (Open)					Condition: 60 ± 2°C (Close)				
		Impurity (%)					Impurity (%)					Impurity (%				
		Pyrrolidone analog	ATV RC H	ATVTHF analog + RC D	Max Ind. Imp	Total impurity	Pyrrolidone analog	ATV RC H	ATVTHF analog + RC D	Max Ind. Imp	Total impurity	Pyrrolidone analog	ATV RC H	ATVTHF analog + RC D	Max Ind. Imp	Total impurity
Precipitated calcium carbonate																
Atorvastatin calcium USP+ Lactose monohydrate + Precipitated calcium carbonate	CS-A001-27	0.04	0.04	0.02	0.01	0.16	0.06	0.05	0.02	0.02	0.27	0.10	0.04	0.02	0.02	0.25
Atorvastatin calcium USP+ Sodium starch glycolate+ Precipitated calcium carbonate	CS-A001-28	0.04	0.04	0.03	0.01	0.17	0.06	0.04	0.01	0.02	0.25	0.44	0.40	0.27	0.10	1.67
Atorvastatin calcium USP+ Croscarmellose sodium+ Precipitated calcium carbonate	CS-A001-29	0.04	0.02	0.02	0.01	0.17	0.05	0.6	0.01	0.02	0.26	0.04	0.04	0.01	0.02	0.18
Atorvastatin calcium USP+ Polysorbate 80 + Precipitated calcium carbonate	CS-A001-30	0.04	0.04	0.02	0.01	0.15	0.45	0.37	0.13	0.16	1.62	0.04	0.04	0.01	0.02	0.20

Table 14: Chemical Characterization (Organic impurities of Initial & 28 days) of Excipient Compatibility Studies

Sample Name	**Sample ID**	**Initial**					**28 days Analysis**					**28 days Analysis**				
		Impurity (%)					**Condition: 40 ± 2°C (Open)**					**Condition: 60 ± 2°C Close)**				
							Organic Impurities (%)					**Organic Impurities (%)**				
		Pyrrolidone analog	ATV RC H	ATV THF analog + RC D	Max Ind. Imp	Total impurity	Pyrrolidone analog	ATV RC H	ATVTHF analog + RC D	Max Ind. Imp	Total impurity	Pyrrolidone analog	ATV RC H	ATV THF analog + RC D	Max Ind. Imp	Total impurity
Atorvastatin calcium USP	CS-A001-01	ND	0.03	0.02	0.06	0.31	0.04	0.06	0.02	0.01	0.17	0.04	0.05	0.02	0.04	0.21
Atorvastatin calcium USP+ Microcrystalline cellulose	CS-A001-14	0.05	0.04	0.02	0.01	0.18	0.05	0.09	0.02	0.04	0.24	0.05	0.06	0.02	0.04	0.21
Atorvastatin calcium USP+ Lactose monohydrate	CS-A001-15	0.05	0.04	0.02	0.01	0.17	0.05	0.21	0.03	0.04	0.38	0.05	0.06	0.02	0.03	0.21
Atorvastatin calcium USP+ Sodium starch glycolate	CS-A001-16	ND	0.04	0.02	0.01	0.12	0.05	0.19	0.02	0.03	0.36	0.04	0.08	0.02	0.04	0.23
Atorvastatin calcium USP+ Croscarmellose sodium	CS-A001-17	ND	0.03	0.03	0.01	0.14	0.05	0.14	0.03	0.04	0.28	0.04	0.07	0.01	0.01	0.19
Atorvastatin calcium USP+ Hydroxypropyl cellulose	CS-A001-18	0.04	0.04	0.02	0.01	0.15	0.05	0.08	0.02	0.04	0.26	0.04	0.06	0.02	0.03	0.20

Sample Name	Sample ID	Initial					28 days Analysis					28 days Analysis				
		Impurity (%)					Condition: 40 ± 2°C (Open)					Condition: 60 ± 2°C Close)				
							Organic Impurities (%)					Organic Impurities (%)				
		Pyrrolidone analog	ATV RC H	ATV THF analog + RC D	Max Ind. Imp	Total impurity	Pyrrolidone analog	ATV RC H	ATVTHF analog + RC D	Max Ind. Imp	Total impurity	Pyrrolidone analog	ATV RC H	ATV THF analog + RC D	Max Ind. Imp	Total impurity
Atorvastatin calcium USP+ Precipitated calcium carbonate	CS-A001-19	0.04	0.03	0.02	0.01	0.15	0.05	0.05	0.02	0.04	0.21	0.04	0.05	ND	0.03	0.17
Atorvastatin calcium USP+ Magnesium stearate	CS-A001-20	0.04	0.04	0.02	0.01	0.15	0.06	0.21	0.02	0.03	0.35	0.05	0.11	0.02	0.03	0.25
Atorvastatin calcium USP+ Polysorbate 80	CS-A001-21	0.04	0.04	0.02	0.01	0.20	0.72	0.61	0.08	0.24	2.55	0.76	0.54	0.07	0.41	2.61
Atorvastatin calcium USP+ Opadry clear (YS-1R-7006)	CS-A001-22	0.04	0.04	0.02	0.01	0.16	0.13	0.10	0.04	0.04	0.46	0.22	0.23	0.03	0.07	0.83
Atorvastatin calcium USP+ Opadry II white (85F18422)	CS-A001-23	0.04	0.04	0.02	0.01	0.16	0.10	0.07	0.02	0.05	0.47	0.40	0.25	0.06	0.27	1.43
Atorvastatin calcium USP+ Hypromellose 2910, 6 cps	CS-A001-24	0.04	0.04	0.02	0.01	0.16	0.04	0.07	0.02	0.01	0.17	0.04	0.05	0.02	0.04	0.19

Sample Name	**Sample ID**	**Initial**					**28 days Analysis**					**28 days Analysis**				
		Impurity (%)					**Condition: 40 ± 2°C (Open)**					**Condition: 60 ± 2°C Close)**				
							Organic Impurities (%)					**Organic Impurities (%)**				
		Pyrrolidone analog	ATV RC H	ATV THF analog + RC D	Max Ind. Imp	Total impurity	Pyrrolidone analog	ATV RC H	ATVTHF analog + RC D	Max Ind. Imp	Total impurity	Pyrrolidone analog	ATV RC H	ATV THF analog + RC D	Max Ind. Imp	Total impurity
Atorvastatin calcium USP+ All Excipient (expected ratio in formulation)	CS-A001-25	0.04	0.04	0.02	0.01	0.15	ND	0.19	0.04	0.17	0.68	ND	ND	ND	ND	ND
Atorvastatin calcium USP+ Microcrystalline cellulose+ Precipitated calcium carbonate	CS-A001-26	0.04	0.04	0.02	0.01	0.15	ND	ND	0.93	ND	0.93	ND	ND	ND	ND	ND
Atorvastatin calcium USP+ Lactose monohydrate + Precipitated calcium carbonate	CS-A001-27	0.04	0.04	0.02	0.01	0.16	0.06	0.06	0.02	0.04	0.29	0.05	0.05	ND	0.04	0.22
Atorvastatin calcium USP+ Sodium starch glycolate+ Precipitated calcium carbonate	CS-A001-28	0.04	0.04	0.03	0.01	0.17	0.07	0.06	0.02	0.04	0.28	0.04	0.06	ND	0.03	0.20

Sample Name	**Sample ID**	**Initial**					**28 days Analysis**					**28 days Analysis**				
		Impurity (%)					**Condition: 40 ± 2°C (Open)**					**Condition: 60 ± 2°C Close)**				
							Organic Impurities (%)					**Organic Impurities (%)**				
		Pyrrolidone analog	ATV RC H	ATV THF analog + RC D	Max Ind. Imp	Total impurity	Pyrrolidone analog	ATV RC H	ATVTHF analog + RC D	Max Ind. Imp	Total impurity	Pyrrolidone analog	ATV RC H	ATV THF analog + RC D	Max Ind. Imp	Total impurity
Atorvastatin calcium USP+ Croscarmellose sodium+ Precipitated calcium carbonate	CS-A001-29	0.04	0.02	0.02	0.01	0.17	0.06	0.06	0.02	0.03	0.24	0.04	0.06	0.01	0.04	0.22
Atorvastatin calcium USP+ Polysorbate 80 + Precipitated calcium carbonate	CS-A001-30	0.04	0.04	0.02	0.01	0.15	0.50	0.36	0.18	0.18	1.72	0.95	0.93	0.13	0.43	3.68

Note: Pyrrolidone analog = Atorvastatin Pyrrolidone Analog, ATV RC H = Atorvastatin Related Compound H, ATV THF analog + RC D =Atorvastatin epoxy THF analog & Atorvastatin Related Compound D, Max Ind. Imp = any other individual unspecified degradation product; ND: Not detected

Inference:

Based on drug-excipient compatibility study results, it is inferring that atorvastatin calcium is incompatible with excipients having peroxide residues (Polysorbate 80, Opadry clear YS-1R-7006, Opadry II white 85F18422) and acidic surface (disintegrating agents) and are chemically compatible Lactose monohydrate, Microcrystalline cellulose, Calcium carbonate, Hydroxypropyl cellulose, Magnesium stearate). However, no incompatibility observed when all excipient are combined with the intended ratio in formulation with API which is probably due to maintaining of alkaline micro environmental pH by calcium carbonate in the dosage form.

2.1.3.2 Excipient and Their Grade Selection for Optimized Formulation

The selection of excipients is vital in the design of a quality drug product and is based not only on their functionality, but also on the compatibility between the drug and the excipients. Excipient-compatibility testing and formulation development studies are used in the selection of the excipient type, grade, and concentration in formulation.

Standard pharmaceutical grade excipients were used and all excipients met compendia standards. Magnesium stearate was used as a lubricant. Magnesium stearate used is from vegetable origin. All the excipients used were certified to be free of melamine and TSE/BSE by the manufacturer. The selection of excipients was depended upon the target profile of drug product. In case of Atorvastatin calcium immediate release tablet, following challenges were considered for selection of the excipient.

- Achieving stability of Atorvastatin calcium trihydrate in dosage form as molecule is unstable in presence of excipient having acidic surface and peroxide residues and need to maintain micro-environmental pH above 8.
- To meet the criteria of size and shape of generic atorvastatin calcium tablets, it was necessary to formulate test product in similar size of RLD. Lipitor® 80 mg tablets available as 19.4mm X 10.5mm dimension having ~1240 mg average weight. Other strengths i.e. 40 mg, 20 mg and 10 mg also proportionally similar with 80 mg.

Table 15: Proposed Inactive Ingredients in Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg

S/N	Name of the Ingredient	Pharmacopoeia Reference	Grade/ Brand	Vendor/ Manufacturer
1.	Microcrystalline Cellulose	USP NF	Vivapur 301	JRS Pharma
2.	Polysorbate 80	USP NF	Kolliphor PS 80	BASF Corporation
3.	Lactose Monohydrate	USP NF	Pharmatose 200M	DFE Pharma
4.	Hydroxypropyl Cellulose	NF	Klucel EF Pharm	Ashland Inc.
5.	Precipitated Calcium Carbonate	USP NF	Sturcal L	Speciality Minerals Lifford
6.	Sodium Starch Glycolate	USP NF	Type A (Primojel®)	DFE Pharma
7.	Croscarmellose Sodium	USP NF	AcDiSol; SD-711	DuPont Nutrition Ireland
8.	Magnesium Stearate	NF	Veg.	Valtris Speciality Chemicals
9.	Opadry II Complete Film Coating System	In House	85F18422; White	Colorcon Asia Pvt. Ltd.
10.	Hypromellose 2910, 6 mPa.s	USP	Pharmacoat 606	Shin-Etsu Chemical Co. Ltd.
11.	Opadry ® Complete Film Coating System	In House	YS-1R-7006; Clear	Colorcon Asia Pvt. Ltd.

Microcrystalline Cellulose (Vivapur 301):

Bulk density of Microcrystalline cellulose (MCC) 301 (B.D: 0.35 – 0.46g/ml) are higher than Microcrystalline cellulose 101 (B.D: 0.26 – 0.31 g/ml), therefore more suitable for top spray granulation of bulky drug substance. In low and high shear processes, MCC allows water to be distributed evenly through the granulation and lends robustness to the process. MCC is very highly compactable and its inclusion can add strength and robustness to a tablet. Additionally, formulations containing MCC are relatively easy to disintegrate (when used with a super disintegrant) leading to the potential for rapid drug dissolution. However, the compactability of MCC is influenced by granulation, and factors that tend to increase the extent of granulation such as increasing amount of water. When the amount of diluent is relatively high then MCC tends to be used in conjunction with another diluent. That's why MCC 301 from JRS Pharma (Vivapur 301) in conjunction with Lactose monohydrate was selected for generic Atorvastatin Calcium Tablets USP.

Lactose Monohydrate (Pharmatose 200M):

Lactose monohydrate is very frequently used in wet granulation, and it is preferable to use milled grades of lactose monohydrate for this purpose. It is known that finer grades of lactose possess improves compaction properties, and the most commonly used grade is "200 mesh" in which the majority of the particles will pass a 75µm sieve. Lactose monohydrate from DFE Pharma (Pharmatose 200M) was selected for generic Atorvastatin Calcium Tablets USP.

Precipitated Calcium Carbonate (Sturcal L):

Achieving stability of Atorvastatin Calcium Trihydrate in dosage form is challenging as molecule is unstable in presence of excipient having acidic surface and oxidative residues and need to maintain micro-environmental pH above 8. To maintain micro environmental pH above 8.0, calcium carbonate (Heavy) was added in formulation.

The Sturcal L precipitated calcium carbonate grades are microcrystalline white powders characterized by their high chemical purity, controlled particle shape and size distribution. Hence, selected for generic Atorvastatin Calcium Tablets USP.

Hydroxypropyl Cellulose (Klucel EF):

Hydroxy propyl cellulose provides premier performance as a tablet binder. Hydroxypropyl Cellulose is a nonionic water-soluble cellulose ether with a remarkable combination of properties and has excellent solubility in water. The viscosity of hydroxy propyl cellulose solutions remains unchanged as pH is varied over the range of 2 to 11. Unmatched tablet hardness and friability are found with low viscosity grades of hydroxy propyl cellulose (Klucel), at typical use levels of 2 to 8%, in a wide variety of processing options.

Grades EF and LF with regular particle size are often used in granulating solutions. Grade Klucel EF from supplier Ashland was selected for generic Atorvastatin Calcium Tablets USP.

Polysorbate 80 (Kolliphor PS 80):

Polysorbate 80 is a synthetic non-ionic, hydrophilic surfactant with broad pH range used as a solubilizing agent in drug formulation. Polysorbate 80 helps for quick "micellar solubilization" of poorly water soluble drug substances at the site of absorption. Kolliphor® PS 80 is an amber liquid with a faint characteristic odor. Polysorbate 80 from BASF (Kolliphor® PS 80) is used as a non-ionic surfactant for generic Atorvastatin Calcium Tablets USP.

Sodium Starch Glycolate Type A (Primojel®):

Sodium Starch Glycolate acts as a superdisintegrant through rapid swelling because of the adsorption of large amounts of water leading to faster disintegration. Sodium Starch Glycolate is the sodium salt of cross-linked carboxymethyl starch and derived from starch with two chemical modifications: substitution (to increase hydrophilicity) and cross-linking (to reduce solubility and gel formation upon contact with water). It is highly effective when used intra-granular and/or extra-granular in dry/wet granulation processes. Two type Sodium Starch Glycolate i.e. type A having pH 5.5-7.5 and type B having pH 3.0-5.0 are available as superdisintegrant. As atorvastatin calcium is sensitive acidic degradation, hence, Sodium Starch Glycolate type A was used as intra-granular disintegrant for generic Atorvastatin Calcium Tablets USP.

Croscarmellose Sodium (Ac-Di-Sol® SD-711):

Croscarmellose Sodium is cross-linked carboxymethylcellulose sodium and used as a superdisintegrant. Croscarmellose Sodium is hydrophilic, but, made insoluble and fibrous by cross-linking of sodium salt of carboxymethylcellulose. The functionality of Croscarmellose Sodium as a superdisintegrant is related to its fluid uptake and swellability characteristics. Swelling, wicking, and strain recovery are proposed mechanisms for Croscarmellose Sodium. Because swelling of Croscarmellose Sodium is attributed to the hydration of the carboxymethyl group, the degree of substitution determines Croscarmellose Sodium functionality in tablet formulations, Croscarmellose Sodium is used at the concentration of 0.5%–5.0% w/w. Any further increase in its level may result in the formation of a viscous gel layer acting as a barrier for disintegration.

Ac-Di-Sol® exhibits consistent critical material attributes such as fibrous morphology, low moisture content, low impurities and low water-soluble content, resulting in robust and reliable performance and Ac-Di-Sol® SD-711 is the premium grade for pharmaceutical applications. As Atorvastatin calcium is sensitive acidic degradation, hence, Croscarmellose Sodium (Ac-Di-Sol® SD-711) was used as extra-granular disintegrant for generic Atorvastatin Calcium Tablets USP.

Magnesium Stearate (Veg):

It is the most commonly used lubricant for tablets. Magnesium stearate is of vegetable origin from supplier Valtris Specialty Chemicals was selected for generic Atorvastatin Calcium Tablets USP.

Opadry II White (85F18422):

Opadry II White is a polyvinyl alcohol based high productivity, water soluble, pH independent complete dry powder film coating system containing polymer, plasticizer and pigment which allows for immediate disintegration for fast, active release. Opadry II White 85F18422 selected for generic Atorvastatin Calcium Tablets USP.

Hypromellose 2910, 6 mPa.s (Pharmacoat 606):

Pharmacoat is a low viscosity hydroxypropyl methylcellulose polymer which is easy to use as a film coating material and gives an excellent finish to the final product. It is versatile and suitable for many applications in the design of film coated tablet formulations. Hypromellose 2910, 6 mPa.s (Pharmacoat 606) used at film coating stage with Opadry II White (85F18422) to prevent pin hole in the coating stage.

Opadry Clear (YS-1R-7006):

Opadry Clear is original, customized, one-step film coating system which combines polymer, plasticizer and pigment, as required, in a dry concentrate. Use of an Opadry film coating will result in attractive, elegant coatings on a variety of tablet cores. Opadry Clear YS-1R-7006 used at final coating for generic Atorvastatin Calcium Tablets USP to provide a gloss to the final tablet in order to improve the appearance.

2.2 Drug Product

2.2.1 Formulation Development

2.2.1.1 Initial Risk Assessment of the Formulation Variables

The results of the initial risk assessment of the formulation variables are presented in Table 16 and the justification for the risk assignment is presented in Table 17.

Table 16: Initial Risk Assessment of the Formulation Variables on Drug Product CQAs

Drug product CQAs	**Formulation Variables**							
	API PSD	**Calcium carbonate amount**	**Diluent type & ratio**	**Disintegrant type & level**	**Binder type & level**	**Surfactant type & level**	**Lubricant type & level**	**Coating material type & level**
Assay	Medium	Medium	Medium	Low	Low	Low	Low	Low
Content Uniformity	High	Medium	Medium	Low	Low	Low	Low	Low
Dissolution	High	High	Medium	High	High	High	High	High
Degradation Products	Low	High	Low	High	Low	High	Low	High

Table 17: Justification for the Initial Risk Assessment of the Formulation Variables on Drug Product CQAs

API Attributes	**Drug Products CQAs**	**Risk Category**	**Justification**
API PSD	Assay	Medium	Particle size distribution may adversely impact uniformity of the drug at granulation stage which can impact the uniformity of the dosage unit for this low API content drug product and in extreme cases, may cause an assay failure. The risk is **Medium** for assay and **High** for content uniformity.
	Content Uniformity	High	
	Dissolution	High	The drug substance is a BCS class II compound; therefore, PSD can affect dissolution. The risk is **High.**
	Degradation Products	Low	Generally, PSD of API is unlikely to impact degradation products. The risk is **Low.**
Calcium carbonate amount	Assay	Medium	Calcium carbonate can impact the flow properties of the dry mixing blend at top spray granulation and ultimately can impact the blend uniformity. Variation in blend uniformity can impact the assay and content uniformity. The risk is **Medium**.
	Content Uniformity	Medium	
	Dissolution	High	The drug substance is a BCS class II compound with low solubility across the physiological pH (pH 1.2-6.8). Solubility of the atorvastatin calcium is pH dependent

API Attributes	**Drug Products CQAs**	**Risk Category**	**Justification**
		🟥	and solubility increases with increase in pH. Calcium carbonate can impact dissolution through maintaining the micro environmental pH of the dosage form. The risk is **High.**
	Degradation Products	High	Atorvastatin calcium sensitive to acid degradation and concentration of calcium carbonate in dosage form is critical to maintain the alkaline pH which will prevent the atorvastatin lactone (Atorvastatin Related Compound H) formation. Hence, the risk is **High.**
Diluent type And ratio	Assay	Medium	Diluent type and ratio can impact the distribution/uniformity of the API at granulation stage which ultimately can impact the dosage form uniformity and assay. For a low-dose formulation, wet granulation helps to fix the API particle within the granulation and thus prevents segregation during processing. Considering the wet granulation process, the risk is **Medium.**
	Content Uniformity	Medium	
	Dissolution	Medium	Diluent type and ratio can impact dissolution via tablet hardness and disintegration. However, tablet disintegration mainly controlled by intra granular and extra granular disintegrating agent. Therefore, the risk is **Medium.**
	Degradation Products	Low	Diluents are compatible with API. The risk is **Low.**
Disintegrant type & level	Assay	Low	Disintegrant type & level is unlikely to impact assay, content uniformity. The risk is **Low.**
	Content Uniformity	Low	
	Degradation Products	High	Disintegrant are acidic in nature which can accelerate the degradation of the atorvastatin calcium by forming atorvastatin lactone (Atorvastatin Related Compound H). The risk is **High.**
	Dissolution	High	Disintegrant type and level can impact the disintegration time and, ultimately dissolution. Since achieving rapid disintegration is important for a drug product containing a BCS class II Compound. The risk is **High.**
Binder type & level	Assay	Low	Binder type & level have no impact on assay and content uniformity. That's why, the risk is **Low**.
	Content Uniformity	Low	
	Degradation Products	Low	Binder can impact the degradation product generation in the dosage form. However, hydroxypropylcellulose (HPC) considered for generic atorvastatin calcium tablets is a

API Attributes	Drug Products CQAs	Risk Category	Justification
			nonionic binder which is prefer for oxidative sensitive molecule and same binder used in reference product. Therefore, the risk is **Low.**
	Dissolution	High	Binder type and level can impact disintegration time of the tablet ultimately can impact the dissolution. API is BCS class II, hence, the risk is **High.**
Surfactant type & level	Assay	Low	In the drug product formulation, surfactant will be used in low concentration and distribution will be ensured by using in binder solution. The risk is **Low.**
	Content Uniformity	Low	
	Dissolution	High	As Atorvastatin is BCS class II molecule. Therefore, surfactant level can impact dissolution, since achieving good dissolution is important. The risk is **High.**
	Degradation Products	High	Polysorbate 80 contains peroxide residue which can accelerate the degradation of the atorvastatin calcium through oxidative degradation. The risk is **High.**
Lubricant type & level	Assay	Low	The concentration of magnesium stearate used is low and its impact on flow is minimal, it is unlikely to impact assay and content uniformity. The risk is **Low.**
	Content Uniformity	Low	
	Dissolution	High	Over-lubrication due to excessive lubricant may retard dissolution. The API is a BCS class II compound. Therefore, the risk is **High.**
	Degradation Products	Low	Magnesium stearate is basic in nature and compatible with API. The risk is **Low.**
Coating Materials type and level	Assay	Low	Generally coating agent do not impact assay and uniformity of the dosage unit. The risk is **Low.**
	Content Uniformity	Low	
	Dissolution	High	High weight gain can increase the disintegration time of the tablets which can impact the dissolution. The risk is **High.**
	Degradation Products	High	Atorvastatin calcium is sensitive to the oxidation stress and functional film coating applied to prevent moisture pick from the environmental condition and to aid in drug product stability. The level of film coating can affect the stability of the dosage form. The risk is **High.**

2.2.1.2 API Particle Size (PSD) Selection for Product Development

Atorvastatin Calcium USP is a BCS class II compound, therefore, PSD can impact dissolution. Additionally, API particle size distribution has a profound impact to the content uniformity in low-dose drug products and micronized particle of API helps to create a homogenous mixture with excipients during processing. API particle size D_{90} not more than 50 µm used for formulation and process development and finally selected for exhibit batches manufacturing with optimized manufacturing process. PSD of the various batches of API of DMF holder found consistent as provided in Table 18.

Table 18: API Batch No. and Particle Size Distribution (PSD)

Batch No.	PSD
ATV4/PDL/198/19	$D_{90:}$ 48.2 µm
ATV4/PDL/199/19	$D_{90:}$ 42.3 µm
ATV4/PDL/200/19	$D_{90:}$ 32.2 µm
3141900140	$D_{90:}$ 16.2 µm
3141900141	$D_{90:}$ 23 µm

2.2.1.3 Process Selection

Wet granulation method is a well-established industrial manufacturing method for tablets and it is more prefer for drug product containing a low dose and API having poor bulk density, flow characteristics. Atorvastatin calcium is a low bulk density, cohesive poorly flowing powder having poor compressibility nature. Poor material flow may produce excessive weight variability for tablets due to uneven distribution of the API, uneven bulk density and eventually uneven filling of die cavities on a tablet press. The materials, which are compressed into tablets, must possess adequate flow-ability, density, and compressibility. This is because the requisite amount of powder mixture required to compress each tablet is filled into the die cavity by volume and not by weight. This requirement of adequate flow-ability, density, and compressibility is particularly important during a high-speed tablet production where the dwell time is often short. For a low-dose formulation, wet granulation helps to fix the API particle within the granulation and thus prevents segregation during processing. Due to low drug load (around 7.3%, w/w) in dosage form, direct compression method is completely ruled out and preferred wet granulation method to control better uniformity of the dosage unit. Both wet high-shear and fluidized-bed technique were utilized during initial formulation and process development but finally fluid bed granulation technique selected to get soft granules with better disintegration and dissolution profile with RLD. Top spray granulation ensures better mixing throughout the granulation process which is prerequisite for better uniformity of the dosage form. This will also improve the flow-ability and compressibility of the powder mixture.

In wet granulation approach, purified water is always a first line of choice due to its inert nature and cost effectiveness. From the literature and chemistry of Atorvastatin Calcium molecule, it can be revealed that API is not sensitive to moisture, based on this scientific rationale and evidence of use of purified water by innovator, same solvent (purified water) was preferred as granulating fluid in wet granulation process for generic atorvastatin calcium tablets.

2.2.1.4 Formulation Development Summary

Formulation development focused on evaluation of the high risk formulation variables as identified in the initial risk assessment shown in Table 16. Formulation development studies were conducted by considering common granulation and blending approach for all strengths to ensure bio waiver for the lower strengths. To develop the stable and bio equivalent formulation of highly variable drug product like atorvastatin calcium tables, concept development was carried out for integrated product and process development. Formulation development for generic atorvastatin calcium tablets are mainly categorized into two parts i.e. prototype formulation development and optimization of the finally selected ingredients. Based on concept development, formulation development for generic atorvastatin calcium is optimized by a systematic approach and formulation development trails pertinent to the decision making process are presented under multiple formulation development studies. Overview of the concept development considered for generic atorvastatin calcium tablets presented below;

Concept design from stability view and for desired bioequivalence of atorvastatin calcium tablets:

Atorvastatin calcium undergoes two major degradation pathways i.e. lactonization and oxidation. Atorvastatin lactone (Atorvastatin Related Compound H) is formed by internal condensation (loss of water) of the alcohol and carboxylic acid to form a six-membered ring. This is the major degradation of atorvastatin calcium can be happened during wet granulation and coated tablet formation, especially in the absence of alkaline earth metal salts. It is well-known that statins are pharmacologically active in the hydroxy acid form, whereas the corresponding lactone form may be considered a pro-drug which may convert to the active hydroxy acid in vivo. The equilibrium between atorvastatin hydroxy acid form, lactone form and inter-conversion kinetics is highly pH dependent as represented in Figure 2.

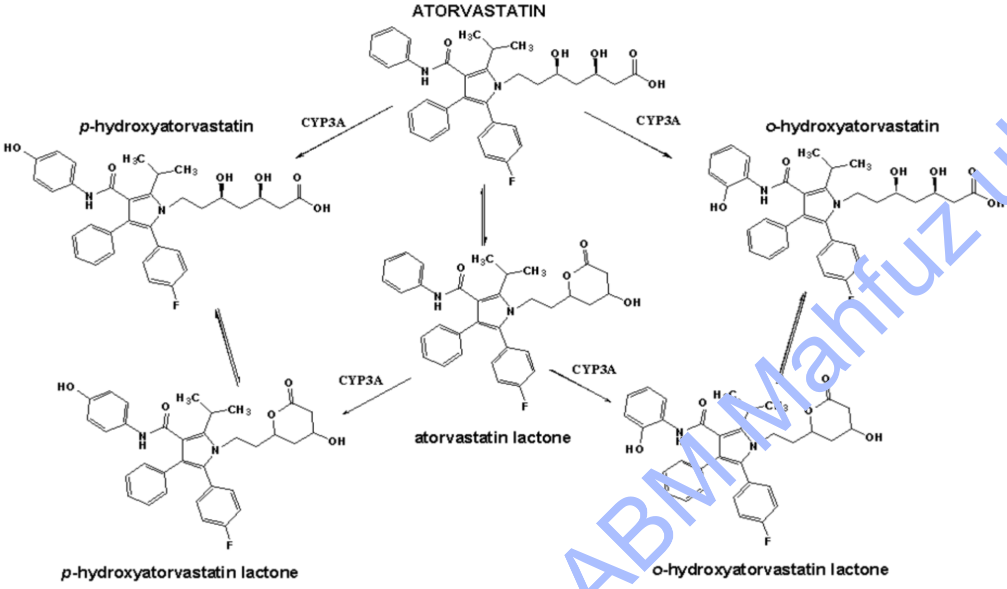

Figure 2: Degradation and metabolic pathway of Atorvastatin Calcium

The acid-catalyzed reaction is reversible, whereas the base catalyzed reaction is practically irreversible: At pH>6, the equilibrium reaction is not detectable and greatly favors the hydroxy acid form. For this reason, it is worthwhile to create a near-neutral or basic microenvironment for atorvastatin in the pharmaceutical composition in order to stabilize the equilibrium *in vivo* i.e. avoid presence of the inactive lactone form with a micro- environment having a pH at or above 6. Moreover, Atorvastatin calcium expected to be dissolved at much faster rates in the case if the tablet capable to increase the pH to a value that meets pKa + 1 of Atorvastatin acid. The pKa of atorvastatin terminal carboxyl group is 4.5. Based on these facts, it is preferred that when pH in the gastric microenvironment equal to or greater than pKa+l, i.e. 4.5+1=5.5. Thus, in order to adjust the basic micro environmental pH for atorvastatin calcium, composition having an “alkalizing agent" to be used in the formulation selected from calcium carbonate &/or other alkalizing agents. While in order to prevent auto oxidation of atorvastatin in dosage form, high level function coating from moisture protective materials can be incorporated in formulation.

For desired bioequivalence, atorvastatin calcium should be immediately released within 5-10 minutes. Accordingly, when atorvastatin calcium is prepared in the form of a tablet, a “disintegrant” is desirable for rapid disintegration of the tablet in the gastrointestinal tract within a pH from 5.5 to 6.8 and thereby assure that the drug is rapidly available for absorption. The most appropriate approach would be to use disintegrant both as intra-granular and extra granular.

Extra-granular disintegrant first disintegrate the whole tablet into individual granules, intra-granular disintegrant finally ensures disintegration of the granules themselves and releasing of the active substance from inside the granules. Thus, at least a disintegrant should be used intra-granular. Once atorvastatin calcium completely released from tablet, the nonionic surfactant (Polysorbate 80) will helps for quick solubilization of atorvastatin calcium at the site of absorption. Commonly, surfactants are defined as substances with both polar (hydrophilic) and non-polar (hydrophobic) groups which are preferentially adsorbed at the interface and exhibit self association in the bulk of the solution at critical micelle concentration (CMC) and form a micelle of colloidal size range with hydrophobic interior and a hydrophilic surface. This hydrophobic pocket inside micelle offer an environment for solubilization of poorly water soluble atorvastatin calcium by micellar solubilization.

2.2.1.4.1 Formulation Development Study 01

Based on the literature review, qualitative reverse engineering of RLD and evaluation of the physicochemical characteristics of RLD seven laboratory scale batches were designed for highest strength (80 mg) with the following goal;

- To see the impact of manufacturing process on drug product CQAs (i.e. dissolution).
- To see the impact of intra-granular diluent and disintegrating agent type and amount on the in process CQAs (i.e. disintegration time) and finished product CQAs (i.e. Assay and dissolution).
- To see the overall impact of selected excipients and their amount on the in-process CQAs as well as on drug product CQAs.

Key formulation variables considered in formulation development study 01 presented in Table 19 and experimental design of the relevant batches provided in Table 20.

Table 19: Key formulation variables considered in formulation development study 01

A. Formulation ingredients considered variables in formulation development study 01

Intragranular disintegrating agent variation		**Diluent type variation**	
Name	**%, w/w**	**Name**	**%, w/w**
Low Hydroxypropyl Cellulose (LH-11)	2.0	Microcrystalline Cellulose-MCC (Vivapur 301)	38.03
Cross povidone (Vivapharm$^{®}$ PVPP XL 10)	2.0	Silicified Microcrystalline Cellulose (SMCC 90)	38.03
Croscarmellose Sodium (AcDiSol; SD-600)	2.0-3.0		
Sodium Starch Glycolate Type A ((Primojel®)	2.0-3.0		

B. Formulation ingredients/process keep constant in formulation development study 01

Particulars	**Ingredients /process**	**%, w/w / ratio**	**Rationale**
Extra-granular disintegrating agent	Croscarmellose Sodium	3.0	Used in RLD and croscarmellose sodium effective at 0.5-5% concentration as disintegrating agent. To get rapid disintegration, concentration at 3.0% w/w considered for initial formulation trails.
Lubricating agent	Magnesium Stearate	0.75	Used in RLD and magnesium Stearate effective at 0.25-2% concentration as lubricant. Considering the low solubility of the API and literature review, 0.75% concentration considered for initial formulation trails.
Surfactant	Polysorbate 80	0.53	Used in RLD and surfactant are generally effective at 0.25-2% concentration for poorly soluble drug. Considering the low solubility of the API and literature review, 0.53% considered for initial formulation trails.
Alkalizing/ pH modifying agent	Calcium Carbonate	23.11	Used in RLD and to maintain micro environmental pH above 8.0, calcium carbonate (Heavy) at 23.11% concentration considered for initial formulation trails.
Binder	Hydroxypropyl Cellulose (Klucel EF)	2.0	Used in RLD and Hydroxypropyl Cellulose effective at 0.5-5% concentration as binder. Considering the diluent quantity and granulation process, 2% w/w concentration for initial formulation trails.
Lactose : MCC/SMCC ratio	-	Ratio: 1: 1.655	Composition used in RLD and ratio selected to get better compactability.
API content	-	7.60	To comply the size and shape requirements for generic products, average weight of the core tablet considered around 1140 mg based on evaluation of the
Granulating Solvent	Purified water	-	Literature data revealed that RLD utilized purified water for wet granulation process
Manufacturing process	High shear wet granulation	-	

Table 20: Experimental Design of the Laboratory Batches of Formulation Development Study 01

			B/N: 18-B-018	**B/N: 18-B-019**	**B/N: 18-B-020**	**B/N: 18-B-021**	**B/N: 18-C-010**	**B/N: 18-C-011**	**B/N: 18-C-012**
Stage	**Ingredient Name**	**Grade &/or Brand**	**(%, w/w)**	**(%, w/w)**	**(%, w/w)**	**(%, w/w)**	**(%, w/w)**	**(%, w/w)**	**(%, w/w)**
Intra-granular	Atorvastatin Calcium Trihydrate	-	7.60	7.60	7.60	7.60	7.60	7.60	7.60
	Precipitated Calcium Carbonate	Sturcal L	23.11	23.11	23.11	23.11	23.11	23.11	23.11
	Lactose Monohydrate	Pharmatose 200 M	22.98	22.56	22.98	22.56	22.98	22.98	22.98
	Microcrystalline Cellulose	Vivapur 301	38.03	37.46	38.03	37.46	38.03	38.03	-
	Silicified Microcrystalline Cellulose	SMCC-90	-	-	-	-	-	-	38.03
	Low Hydroxypropyl Cellulose	LH-11	-	-	-	-	2.00	-	-
	Crosspovidone	Vivapharm® PVPP XL 10	-	-	-	-	-	2.00	-
	Croscarmellose Sodium	AcDiSol; SD-600	2.00	3.00	-	-	-	-	2.00
	Sodium Starch Glycolate Type A	(Primojel®)	-	-	2.00	3.00	-	-	-
	Polysorbate 80	Kolliphor PS 80	0.53	0.53	0.53	0.53	0.53	0.53	0.53
	Hydroxypropyl Cellulose	Klucel LF Pharm	2.00	2.00	2.00	2.00	2.00	2.00	2.00
	Purified Water #	NA	QS	QS	QS	QS	QS	QS	QS
Extra-granular	Magnesium Stearate	Veg.	0.75	0.75	0.75	0.75	0.75	0.75	0.75
	Croscarmellose Sodium	AcDiSol; SD-600	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Total Core Tablet Weight (%)			100.00	100.00	100.00	100.00	100.00	100.00	100.00

# Purified water evaporates during drying process and not a part of final product.

Table 21: Brief Manufacturing Procedure of Laboratory Batches Manufactured under Formulation Development Study 01

Batch No.	Strength	Unit Operations	Specifications/Controls
18-B-018, 18-B-019, 18-B-020, 18-B-021, 18-C-010, 18-C-011, 18-C-012	80 mg	Co-Sifting and Sifting	**Mesh used:** # 24 (Co-sift Atorvastatin calcium and Precipitated calcium carbonate)
			Mesh used: # 24 (Sift Microcrystalline Cellulose, Lactose Monohydrate and Croscarmellose Sodium/Sodium Starch Glycolate)
		Wet Granulation	**Equipment used:** Gansons High Shear Granulator (RMG)
			RMG Bowl used: 5 L
			Dry mixing: Time-5 Min; Impeller Speed- 350 RPM
			Wet mixing: Time- 2 Min; Impeller Speed- 350 RPM; Chopper Speed- 1440 RPM; Dosing- 50 RPM
			Kneading: Time- 2 Min Impeller Speed- 350 RPM
		Drying	**Equipment used:** Fluid Bed Processor
			Product container used: 7 L
			Inlet air temperature: 65 ± 10ºC
			Product temperature: 30 ± 5ºC
		Size Reduction	**Equipment used:** Oscillating Granulator
			Screen size: 1.5 mm
			Milling Time: 3 Min
			Milling Speed: 50 RPM
		Blending and Lubrication	**Equipment used:** Bin Blender
			Mesh used for sifting of the extra-granular blending and lubricating materials: # 40
			Bin used: 5 L
			Blender speed (RPM): 10
			Total Blending Time: 10 min
			Blending Time: 7 min (70 revolutions)
			Lubrication Time: 3 min (30 revolutions)
		Compression	**Equipment Used:** Tablet Compression Machine
			Tooling: 19.30 X 10.35 mm, Oval shape (80 mg)
Ref. LNB		**R&D/0042**	

Table 22: Summary of Physicochemical Parameter of Formulated Batches Manufactured under Formulation Development Study 01

Batch No.	**Strength**	**Disintegration Time Target: NMT 15 minutes (without disc)**		**% Assay (Limit: NLT 94.5% and NMT 105.0% of the labeled amount of Atorvastatin)**	**% Dissolution (pH 6.8 Phosphate Buffer; Paddle; 900 ml; 75 RPM; Time point: 30 min)**		
		FT	**LT**		**Avg.**	**Min.**	**Max.**
18-B-018	80 mg	2'35"	2'45"	99.2	92	89	94
18-B-019		3'0"	3'15"	99.9	90	76	95
18-B-020		2'55"	2'58"	99.4	92	91	94
18-B-021		3'05"	3'22"	101.1	89	87	90
18-C-010		2’40”	3’10”	100.7	84	83	85
18-C-011		3’05”	3’15”	98.5	72	70	74
18-C-012		3’10”	3’25”	102.2	93	90	96
Ref. LNB		**R&D/0042; R&D/0019; R&D/0028**					

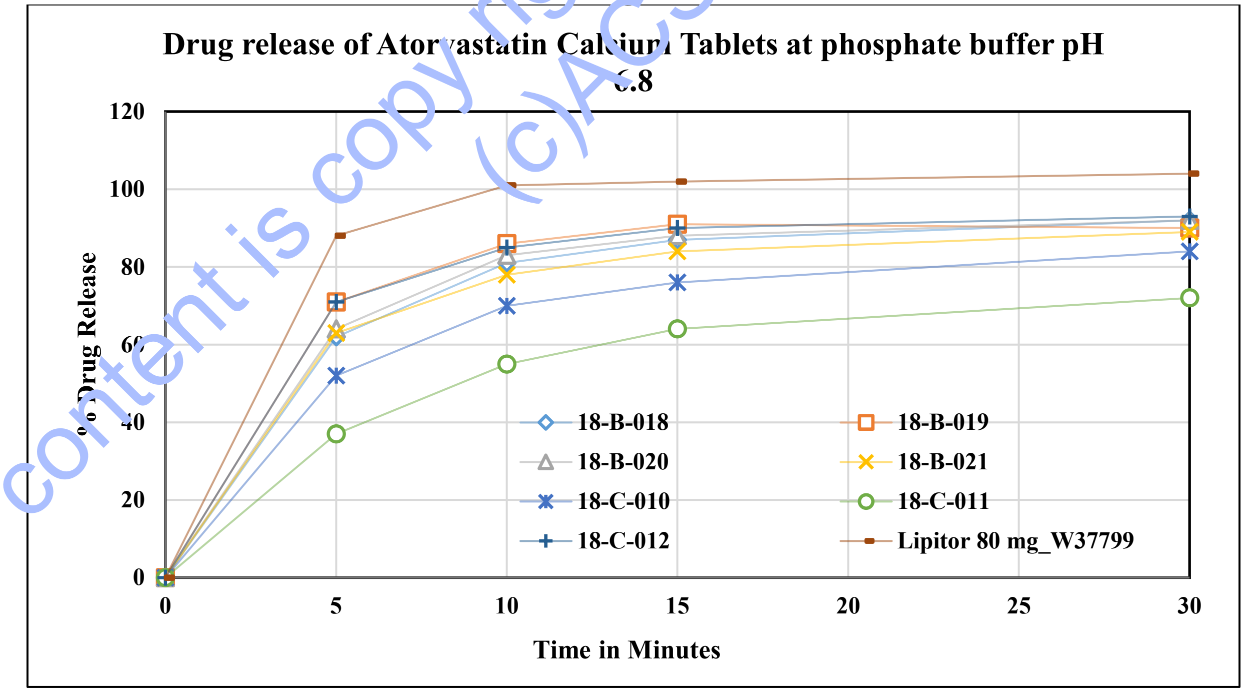

Figure 3: Comparative release profile for different batches of Atorvastatin Calcium Tablets with RLD (Lipitor 80 mg) at phosphate buffer pH 6.8

Inference:

Based on the evaluation of physicochemical results of the batches manufactured in the formulation development study 01, below outcomes were concluded.

- All tablets had disintegration time within 5 minutes.
- The assay content of all formulations was within 98.5-102.2% which indicates wet granulation process feasible for manufacturing of Atorvastatin Calcium tablets.
- Slower drug release observed for the batches manufactured with Low hydroxypropyl cellulose (B/N: 18-C-010) and Crospovidone (B/N: 18-C-011) where less than 85% of the drug were released within 30 minutes at OGD method.
- Batches manufactured with Croscarmellose Sodium (B/N: 18-B-018, 18-B-019 and 18-C-012) and Sodium starch glycolate (B/N: 18-B-020 and 18-B-021) showed that more than 85% of the drug was released within 30 minutes at OGD method.

Dissolution profile of the formulated batches does not match with the innovator product. To increase the dissolution rate further study was considered by using top spray granulation (FBP) instead of high shear granulation (RMG) as fluid bed granulation generate porous granules with better disintegration properties.

2.2.1.4.2 Formulation Development Study 02

Based on outcome of formulation development study 01, two intragranular disintegrating agents i.e croscarmellose sodium and sodium starch glycolate type A has been selected to conduct formulation development trails at this study for all strength using top spray granulation (FBP) process with following goal;

- To see the impact of different wet granulation process (high shear vs. top spray granulation) on drug release.
- To select the optimum intra-granular disintegrating agent.

Experimental design of the relevant batches provided under formulation development study 02 presented in Table 23.

Table 23: Experimental Design of the Laboratory Batches of Formulation Development Study 02

			B/N: 18-C-009					**B/N: 18-C-027**				
Stage	**Ingredient Name**	**Grade &/or Brand**	**Qty/ Tablet (80 mg)**	**Qty/ Tablet (40 mg)**	**Qty/ Tablet (20 mg)**	**Qty/ Tablet (10 mg)**	**(% w/w)**	**Qty/ Tablet (80 mg)**	**Qty/ Tablet (40 mg)**	**Qty/ Tablet (20 mg)**	**Qty/ Tablet (10 mg)**	**(% w/w)**
Intra-granular	Atorvastatin Calcium Trihydrate	-	86.60	43.30	21.65	10.83	7.25	86.60	43.30	21.65	10.83	7.25
	Precipitated Calcium Carbonate	Sturcal L	263.50	131.75	65.88	32.94	22.06	263.50	131.75	65.88	32.94	22.06
	Lactose Monohydrate	Pharmatose 200 M	262.00	131.00	65.50	32.75	21.93	262.00	131.00	65.50	32.75	21.93
	Microcrystalline Cellulose	Vivapur 301	433.55	216.78	108.39	54.19	36.29	433.55	216.78	108.39	54.19	36.29
	Croscarmellose Sodium	AcDiSol; SD-600	-	-	-	-	-	22.80	11.40	5.70	2.85	1.91
	Sodium Starch Glycolate Type A	(Primojel®)	22.80	11.40	5.70	2.85	1.91	-	-	-	-	-
	Polysorbate 80	Kolliphor PS 80	6.00	3.00	1.50	0.75	0.50	6.00	3.00	1.50	0.75	0.50
	Hydroxypropyl Cellulose	Klucel LF Pharm	22.80	11.40	5.70	2.85	1.91	22.80	11.40	5.70	2.85	1.91
	Purified water#	N/A	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
Extra-granular	Magnesium Stearate	Veg.	8.55	4.28	2.14	1.07	0.72	8.55	4.28	2.14	1.07	0.72
	Croscarmellose Sodium	AcDiSol; SD-600	34.20	17.10	8.55	4.28	2.86	34.20	17.10	8.55	4.28	2.86
Total Core Tablet Weight (mg)			**1140.00**	**570.00**	**285.00**	**142.50**	**-**	**1140.00**	**570.00**	**285.00**	**142.50**	**-**
Coating	Opadry AMB II* (88A180021)	N/A	43.84	21.92	10.96	5.48	3.70	43.84	21.92	10.96	5.48	3.70
	Purified water#	N/A	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total Coated Tablet Weight (mg)			**1183.84**	**591.92**	**295.96**	**147.98**	**100.00**	**1183.84**	**591.92**	**295.96**	**147.98**	**100.00**

# Purified water evaporates during drying process and not part of final product. *20% overage considered to compensate process loss.

Table 24: Brief Manufacturing Procedure of Formulated Batches Manufactured under Formulation Development study 02

Batch No.	Strength	Unit Operations	Specifications/Controls
18-C-009, 18-C-027 (Common Blend)	80 mg, 40 mg, 20 mg & 10 mg	Co-Sifting and Sifting	**Equipment used:** Vibratory Sifter
			Mesh used: # 24 (Co-sift Atorvastatin calcium and Precipitated calcium carbonate)
			Mesh used: # 24 (Sift Microcrystalline Cellulose, Lactose Monohydrate and Croscarmellose Sodium/Sodium Starch Glycolate)
		Drying	**Equipment used:** Fluid Bed Processor
			Inlet air temperature: 55 ± 10°C
			Atomizing air pressure (bar): 1± 0.3
			Drying Time: 10 Min
		Top Spray Granulation	**Equipment used:** Fluid Bed Processor
			Product container Used: 8 L
			Inlet air temperature: 65 ± 10°C
			Solution pump speed (RPM): 15±5
			Atomizing air pressure (bar): 1± 0.3
		Blending and Lubrication	**Equipment used:** Bin Blender
			Mesh used for sifting of the extra-granular blending and lubricating materials: # 40
			Bin used: 5 L
			Blender speed (RPM): 10
			Blending Time: 7 min (70 revolutions)
			Lubrication Time: 3 min (30 revolutions)
		Compression	**Equipment Used:** Tablet Compression Machine
			Tooling: 19.30 X 10.35 mm, Oval shape (80 mg), 15.50 X 8.15 mm, Oval shape (40 mg), 12.30 X 6.40 mm, Oval shape (20 mg) and 9.80 X 5.10 mm, Oval shape (10 mg)
		Coating	**Equipment Used:** Huttlin Drum coater
Ref. LNB	**R&D/0042**		

Table 25: Summary of Physicochemical Parameter of Formulated Batches Manufactured under Formulation Development study 02

Batch No.	Strength	Disintegration Time Target: NMT 15 minutes (without disc)		% Dissolution (pH 6.8 Phosphate Buffer; Paddle; 900 ml; 75 RPM; (Time point: 30 min)		
		FT	LT	Avg.	Min.	Max.
18-C-009-A	80 mg	2'10"	2'13"	100	98	101
18-C-009-B	40 mg	1'52"	2'05"	95	93	97
18-C-009-C	20 mg	1'27"	1'37"	97	96	98
18-C-009-D	10 mg	-	-	100	99	102
18-C-027-A	80 mg	2'30"	3'0"	98	96	99
18-C-027-B	40 mg	1'45"	2'0"	96	94	97
18-C-027-C	20 mg	1'24"	1'34"	101	99	102
18-C-027-D	10 mg	-	-	102	100	106
Ref. LNB		**R&D/0042; R&D/0027; R&D/0028**				

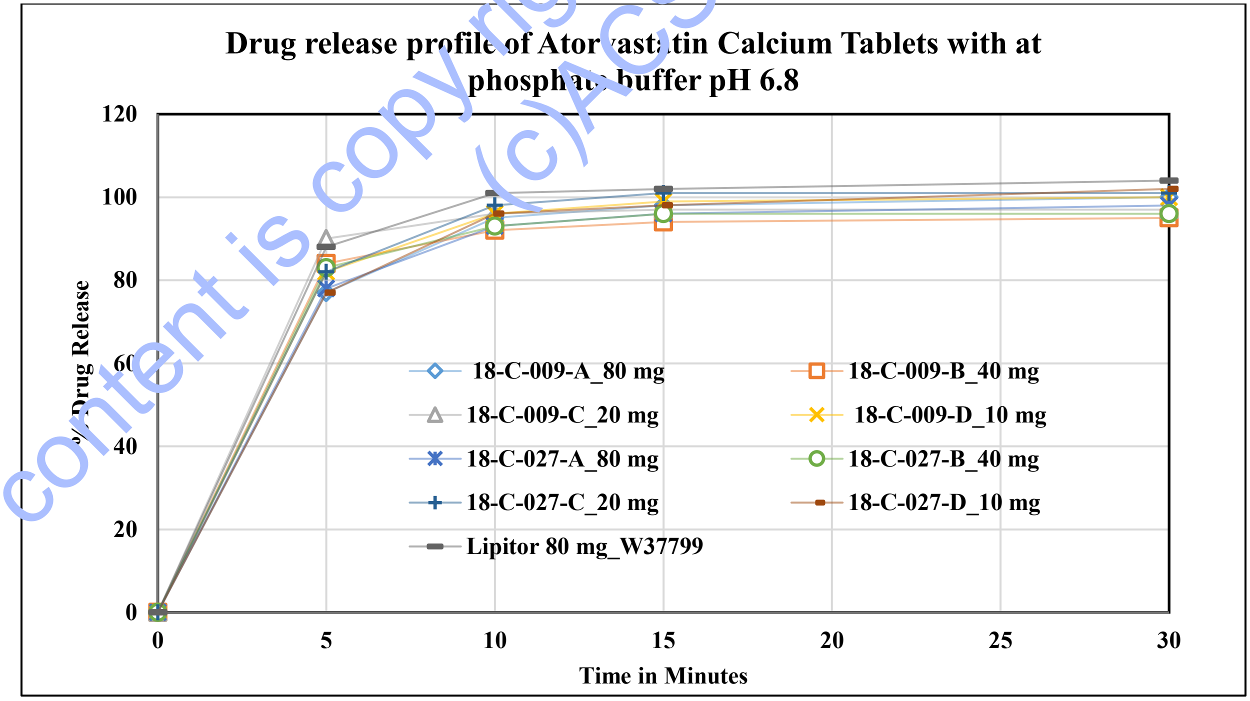

Figure 4: Comparative release profile for different batches of Atorvastatin Calcium Tablets with RLD (Lipitor 80 mg) at phosphate buffer pH 6.8

Inference:

Based on the evaluation of physicochemical data of the batches manufactured in the formulation development study 02, below outcomes were concluded.

- All batches of different strengths had disintegration time within 5 minutes.
- Batches manufactured with intra-granular sodium starch glycolate (B/N: 18-C-009) and croscarmellose sodium (B/N: 18-C-027) showed that more than 85% of the drug was released within 30 minutes. As atorvastatin calcium is sensitive acidic degradation and degree of substitution of croscarmellose sodium is higher than that of sodium starch glycolate. Hence, Sodium Starch Glycolate type A having pH 5.5-7.5 was used as intra-granular disintegrant for generic Atorvastatin Calcium tablets.
- Similar dissolution profile found across all strengths at OGD media.
- Dissolution profile of bio strength (80 mg) of generic atorvastatin calcium tablets manufactured by top spray granulation process comparable with RLD (Lipitor 80 mg tablet). Hence, top spray granulation considered feasible manufacturing process for generic atorvastatin tablets.
- Rough surface/pin hole of the tablets noticed after film coating especially for highest strength (80 mg). The potential cause of pin hole probably due to lower viscosity of the coating suspension and/ or because of foam produced by spray atomization of the coating solution.

2.2.1.4.3 Formulation Development Study 03

The purpose of formulation development study 03 is to take a trail for atorvastatin calcium tablets, 80 mg with similar qualitative composition (core tablets) of batch 18-C-009 from formulation development study 02 considered with minor adjustment in quantitative composition to evaluate the suitability of manufacturing and stability of the chosen formulation prior to upscale / exhibit batch of the final product. In addition, the primary packaging material for atorvastatin calcium tablets was evaluated.

To increase the viscosity of the coating suspension, combination of Hypromellose 2910, 6 cps with ready mix Polyvinyl Alcohol (PVA) based coating materials (Opadry AMB II 88A180021) considered for film coating of the core tablets and finally tablets are gloss coated Opadry Clear YS-1R-7006 to get acceptable appearance of the final coated tablets.

Table 26: Batch Manufacturing Formula for Formulation Development Study 03

			B/N: 18-G-018		
Stage	**Ingredient Name**	**Grade &/or Brand**	**Qty/ Tablet (80 mg)**	**Qty/ Tablet (10 mg)**	**(% w/w)**
Intra-granular	Atorvastatin Calcium Trihydrate	-	86.60	10.83	7.24
	Precipitated Calcium Carbonate	Sturcal L	247.30	30.91	20.68
	Lactose Monohydrate	Pharmatose 200 M	271.10	33.89	22.67
	Microcrystalline Cellulose	Vivapur 301	447.00	55.88	37.37
	Sodium Starch Glycolate Type A	Primojel®	31.60	3.95	2.64
	Polysorbate 80	Tween 80	6.05	0.76	0.51
	Hydroxypropyl Cellulose	Klucel LF Pharm	23.00	2.88	1.92
	Purified Water#	N/A	QS	QS	QS
Extra-granular	Magnesium Stearate	Veg.	5.75	0.72	0.48
	Croscarmellose Sodium	AcDiSol; SD-711	31.60	3.95	2.64
Total Core Tablet Weight (mg)			**1150.00**	**143.75**	**96.15**
Coating	Opadry AMB II (88A180021)*	N/A	40.25	5.03	3.37
	Hypromellose 2910, 6 cps*	Pharmacoat 606	2.88	0.36	0.24
	Opadry Clear (Clear; YS-1R-7006)*	N/A	2.88	0.36	0.24
Total Coated Tablet Weight (mg)			**1196.00**	**149.50**	**100.00**

* 10% overage consider to compensate process loss. # Purified water evaporates during drying process and not a part of final product.

Table 27: Brief Manufacturing Procedure of Batch No. 18-G-018

Batch No.	**Strength**	**Unit Operations**	**Specifications/Controls**
18-G-018 (Common Blend)	80 mg and 10 mg	Co-Sifting and Sifting	**Equipment used:** Vibratory Sifter
			Mesh used: # 24 (Co-sift Atorvastatin calcium and Precipitated calcium carbonate)
			Mesh used: # 24 (Sift Microcrystalline Cellulose, Lactose Monohydrate and Sodium Starch Glycolate)
		Pre-mixing	**Equipment used:** Bin Blender
			Bin used: 10 L
			Blender speed (RPM): 10
			Mixing time: 5 Min
		Top Spray Granulation	**Equipment used:** Fluid Bed Processor
			Product container Used: 8 L
			Inlet air temperature: 65 ± 10ºC
			Solution pump speed (RPM): 15
			Atomizing air pressure (bar): 1± 0.3
		Blending and Lubrication	**Equipment used:** Bin Blender
			Mesh used for sifting of the extra-granular blending and lubricating materials: # 40
			Bin used: 5 L
			Blender speed (RPM): 10
			Blending Time: 7 min (70 revolutions)
			Lubrication Time: 2 min (20 revolutions)
		Compression	**Equipment Used:** Tablet Compression Machine
			Tooling: 19.30 X 10.35 mm, Oval shape (80 mg), 9.80 X 5.10 mm, Oval shape (10 mg)
		Coating	**Equipment Used:** Huttlin Drum coater
Ref. LNB		**R&D/0042**	

Table 28: Summary of Physicochemical Parameter of Formulation Development Study 03 (Core Tablet)

Batch No.	**Strength**	**Hardness (kp)**			**Avg. weight (mg)**			**Disintegration Time Target: NMT 15 minutes (without disc)**
		Avg.	**Min**	**Max**	**Avg.**	**Min**	**Max**	
18-G-018	80 mg	19.81	18.26	21.41	1154.4	1147.6	1168.3	2 min 10 sec
Ref. LNB		**R&D/0042**						

Table 29: Comparative dissolution profile of RLD vs. formulated Batch No. 18-G-018 at USP dissolution media, pH 6.8.

Dissolution Media	pH 6.8 Phosphate Buffer							
Apparatus	Paddle (USP Apparatus II)							
Volume	900 mL							
Speed	75 RPM							
Proposed Specification	NLT 80% (Q) dissolved in 30 minutes							
Time (Minute)	**W37799**				**18-G-018**			
	Avg.	Min	Max	% RSD	Avg.	Min	Max	% RSD
5	88	84	93	3.8	84	78	88	3.7
10	101	98	106	2.2	94	90	96	2.2
15	102	101	105	1.4	96	94	98	1.2
30	104	102	106	1.4	99	98	100	0.6
Ref. LNB	**R&D/0061, R&D/0076**							

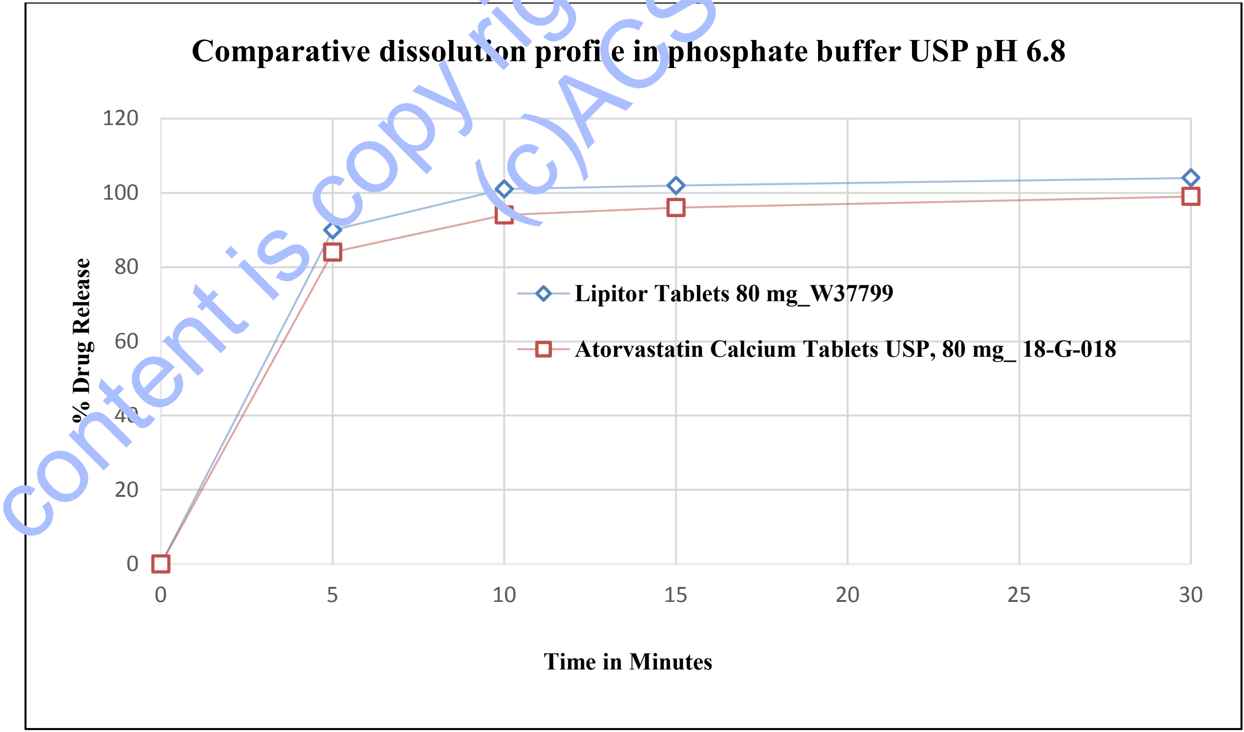

Figure 5: Comparative dissolution Profile in Phosphate buffer USP pH 6.8

Table 30: Summary of Stability Study of Batch No.: 18-G-018 Manufactured under Development Study 03

S/N	Tests	Initial	**Packaging Configuration:** 200 CC 38 mm CRC; 1g silica canister in each container			
			2 Months		**3 Months**	
			200 cc 25°C/ 60% RH	**200 cc 40°C/ 75% RH**	**200 cc 25°C/ 60% RH**	**200 cc 40°C/ 75% RH**
1	Description/ Visual Examination: White to off white, oblong shape tablets having embossing AHI on onside and 80 on other side.	Complies	Complies	Complies	Complies	Complies
2	Water Content by KF (%, w/w)	3.28	3.67	3.66	3.61	3.98
3	Assay (%)	102.3	103.0	103.4	100.3	102.5
4	Organic Impurities by HPLC (%)					
4.1	Atorvastatin pyrrolidone analog	0.10	0.08	0.10	0.09	0.12
4.2	Atorvastatin related compound H	0.06	0.08	0.11	0.07	0.12
4.3	Atorvastatin epoxy pyrrolooxazin 6-hydroxy analog	0.11	ND	0.06	ND	0.11
4.4	Atorvastatin epoxy pyrrolooxazin 7-hydroxy analog	ND	ND	ND	ND	ND
4.5	Atorvastatin epoxy THF analog	ND	0.01	ND	ND	ND
4.6	Atorvastatin related Compound D	0.01	0.03	0.04	0.01	0.04
4.7	Any other unspecified degradation product	0.02	0.06	0.04	0.07	0.03
4.8	Total impurity	0.34	0.31	0.40	0.28	0.48
5	Dissolution: (pH 6.8 Phosphate Buffer, 900 mL, USP Apparatus II, 75 RPM)	96 % (94~98)	95 % (93~96)	95 % (90~98)	96 % (95~98)	91 % (88~96)
Ref. LNB		**R&D/0061, R&D/0066, R&D/0076**				

Inference:

Formulation composition, manufacturing process and container closure systems considered for the batch 18-G-018 met predefined quality attributes of drug product. Based on satisfactory stability study results as well as comparable release profile with RLD, this batch was sent to conduct pilot bio equivalence study to get the idea of the sample size and study design at pivotal scale bioequivalence study for this highly variable drug product.

Summary of Pilot Fasting State BE:

Reference product: Lipitor® (Atorvastatin Calcium) Tablets, 80 mg by UPJOHN MANUFACTURING IRELAND UNLTD (Formerly Pfizer Inc.)

Lot No: W37799 (Expiry: August 2020)

Test product: Atorvastatin Calcium Tablets USP, 80 mg

Batch No: 18-G-018 (Manufacturing date: July, 2018)

Study No: BE/18/509

Table 31: Summary Pharmacokinetic Parameters of Pilot BE Study (Under Fasting Condition)

Pharmacokinetic Parameters	**Ratio, 90 % C.I, Intra-Subject % CV**		
	Ratio (T/R)	**90 % C.I**	**Intra-Subject % CV**
Cmax (ng/mL)	111.47%	93.09- 133.49	28.35%
AUC$_{(0-t)}$ (ng.h/mL)	118.46%	103.21 -135.96	21.50%
AUC$_{(0-inf)}$ (ng.h/mL)	118.04%	103.45- 134.69	20.57%

PK Ratio (A With B) of Atorvastatin for Parameters C$_{max}$, AUC$_{0-t}$ and AUC$_{0-inf}$

Subject	**C$_{max}$**	**AUC$_{0-t}$**	**AUC$_{0-inf}$**
1	95.13	78.77	79.72
2	137.25	198.99	196.22
3	117.08	161.98	162.83
4	102.59	153.01	146.72
5	155.93	123.45	123.54
6	118.41	96.68	92.66
7	50.02	69.16	71.82
8	204.24	148.13	148.33
9	62.06	135.31	132.92
10	105.97	107.95	107.55
11	276.05	219.05	218.29
12	164.71	114.98	114.56
13	115.34	112.70	113.76
15	75.31	82.19	81.91
16	83.05	92.47	93.96
N	**15**	**15**	**15**
Mean	**124.21**	**126.32**	**125.65**
SD	**58.27**	**43.57**	**42.73**
Min	**50.02**	**69.16**	**71.82**
Median	**115.34**	**114.98**	**114.56**
Max	**276.05**	**219.05**	**218.29**
CV%	**46.91**	**34.49**	**34.01**

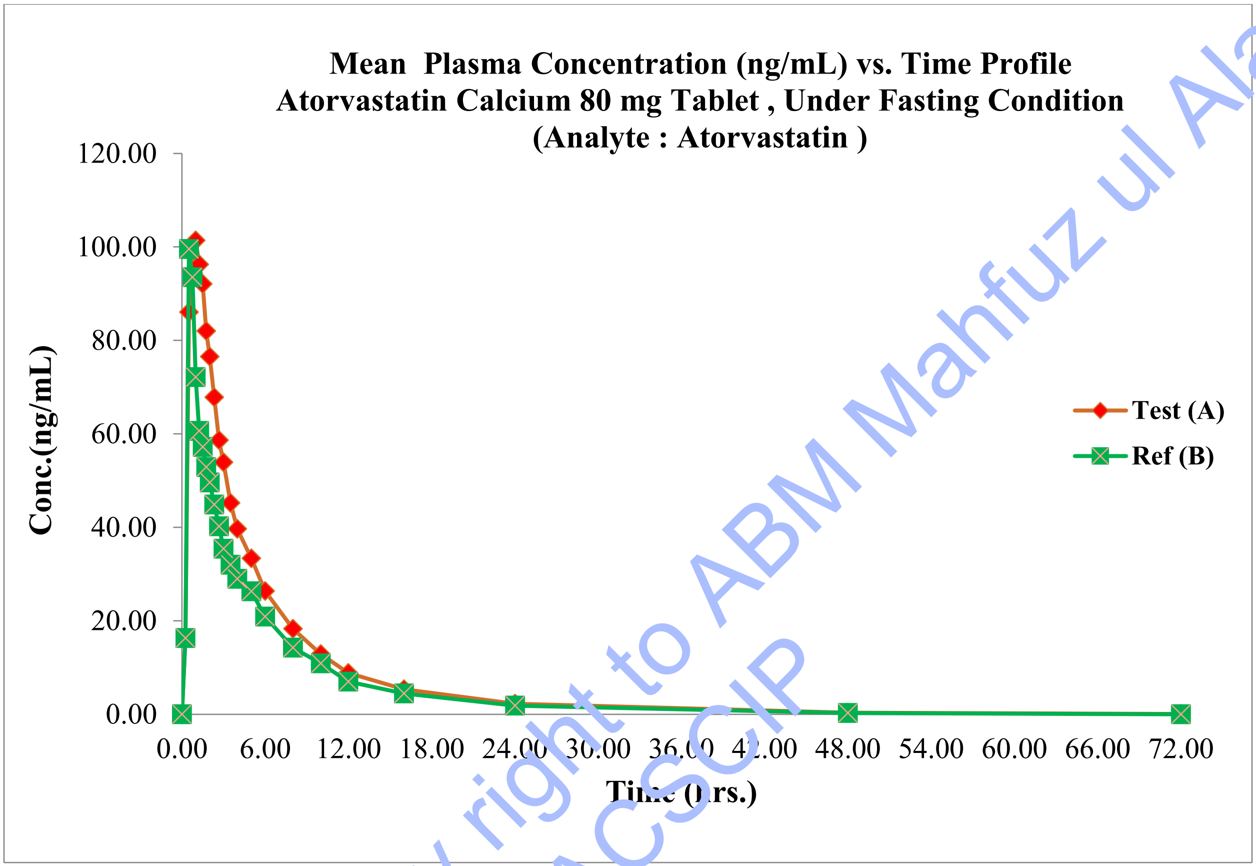

Figure 6: Plasma Drug Concentration versus Time Profiles of the Test Product (Atorvastatin Calcium Tablet USP, 80 mg) vs. RLD (Lipitor 80 mg tablets) at Pilot Fasting State BE

Inference:

Although 90% CI observed wider and was not fall within BE limit 80-125% but Test/Reference ratio of PK parameters of this study at 111.47- 118.46% is promising for pivotal BE passing with adequate sample size and study design recommended in product specific guidance of atorvastatin calcium tablets. From individual PK Ratio (Test with Ref) of Atorvastatin calcium for Parameters C_{max}, AUC_{0-t} and AUC_{0-inf} and Intra-Subject % CV, it can be concluded variability observed in PK parameters is intrinsic to the drug rather than formulation attributes in this study.

2.2.1.4.4 Formulation Development Study- 04

Based on evaluation of the prototype stability data, *in-vivo* results and outcomes of manufacturing process at formulation development study 01 to study 03, laboratory scale trails conducted with minor adjustment in quantitative composition at core stage and qualitative composition change in coating stage to derive the final prototype formulation for formulation optimization and process characterization study. Finally, selected formulation composition has been presented in Table 32 and this optimized formulation was stress tested to compare the degradation product with the batch evaluated at up-front stability study (B/N: 18-G-018). Summary of the stress testing has been presented in Table 35 (for 10 mg) and Table 36 (for 80 mg).

Table 32: Batch Manufacturing Formula for Formulation Development Study 04

			B/N: 20-F-014		
Stage	**Ingredient Name**	**Grade &/or Brand**	**Qty/ Tablet (80 mg)**	**Qty/ Tablet (10 mg)**	**(% w/w)**
Intra-granular	Atorvastatin calcium Trihydrate	N/A	86.60	10.83	7.53
	Precipitated Calcium Carbonate	Sturcal L	258.75	33.34	22.50
	Lactose Monohydrate	Pharmatose 200 M	270.00	33.75	23.48
	Microcrystalline Cellulose	Vivapur 301	439.78	54.97	38.24
	Sodium Starch Glycolate Type A	Primojel®	28.75	3.59	2.50
	Polysorbate 80	Kolliphor PS 80	2.88	0.36	0.25
	Hydroxypropyl Cellulose	Klucel EF Pharm	28.75	3.59	2.50
	Purified Water#	N/A	QS	QS	QS
Extra-granular	Magnesium Stearate	Veg.	8.63	1.08	0.75
	Croscarmellose Sodium	AcDiSol; SD-711	28.75	3.59	2.50
Total Core Tablet Weight (mg)			**1150.00**	**143.75**	**100.00**
Coating	Opadry II White (88A180021)*	N/A	40.25	5.03	-
	Hypromellose 2910, 6 cps*	Pharmacoat 606	2.88	0.36	-
	Opadry Clear (Clear; YS-1R-7006)*	N/A	2.88	0.36	-
Total Coated Tablet Weight (mg)			**1196.00**	**149.50**	**-**

#Purified water evaporates during drying process and not part of final product *20% overage consider to compensate process loss.

Table 33: Brief Manufacturing Procedure of Formulated Batches Manufactured under Formulation Development Study 04

Batch No.	**Strength**	**Unit Operations**	**Specifications/Controls**
20-F-014 (Common Blend)	80 mg & 10 mg	Co-Sifting and Sifting	**Mesh used:** # 24 (Co-sift Atorvastatin calcium and Precipitated calcium carbonate)
			Mesh used: # 24 (Sift Microcrystalline Cellulose, Lactose Monohydrate and Sodium Starch Glycolate)
		Top Spray Granulation	**Equipment used:** Fluid Bed Processor
			Product container Used: 8 L
			Inlet air temperature: 70 ± 10ºC
			Solution pump speed (RPM): 15 ± 10
			LOD: NMT 2.08%
			Drying time: 20 Min
		Blending and Lubrication	**Equipment used:** Bin Blender
			Mesh used for sifting of the extra-granular blending and lubricating materials: # 40
			Bin used: 10 L
			Blender speed (RPM): 15
			Blending Time: 10 min (100 revolutions)
			Lubrication time : 5 min (50 revolutions)
		Compression	**Equipment Used:** Tablet Compression Machine
			Tooling: 19.30 X 10.35 mm, Oval shape (80 mg), 9.80 X 5.10 mm, Oval shape (10 mg)
		Coating	**Equipment Used:** Gansons coater
Ref. LNB			**R&D/0217**

Table 34: Physical Characterization of Atorvastatin calcium Tablets USP, 80 mg and 10 mg of Study 04 (Core Tablet)

Batch No	**Strength**	**Weight Variaiton (mg)**			**Hardness (Kp)**			**Disintegration Time (without disc)**		**Friability (%)**
		Min.	**Max.**	**Avg.**	**Min.**	**Max**	**Avg.**	**FT**	**LT**	
20-F-014-A	10 mg	145.02	150.66	148.29	6.49	9.23	7.89	53”	1’06”	0.15
20-F-014-B	80 mg	1145.00	1169.55	1153.82	15.75	21.61	19.74	1’52”	2’01”	0.02
LNB Ref.		**R&D/0217**								

Table 35: Stress Testing Results of Batch No.: 20-F-014-A (10 mg) Manufactured under Development Study 04

Tests/Specifications	**Initial**	**Packaging Configuration:** 40CC HDPE container with 33mm CRC (without desiccant)					
		7 days	**7 days**	**7 days**	**14 days**	**14 days**	**14 days**
		40°C/75%RH (Open)	**40°C/75%RH (Close)**	**60°C (Close)**	**40°C/75%RH (Open)**	**40°C/75%RH (Close)**	**60°C (Close)**
Organic Impurities by HPLC							
Atorvastatin pyrrolidone analog; NMT 0.5 %	0.05 %	0.08 %	0.07 %	0.12 %	0.08 %	0.06 %	0.16 %
Atorvastatin related compound H; NMT 1.0 %	0.04 %	0.07 %	0.06 %	0.15 %	0.02 %	0.02 %	0.17 %
Atorvastatin epoxypyrrolooxazin 6-hydroxy analog; NMT 0.5 %	ND	0.03 %	ND	ND	ND	ND	ND
Atorvastatin epoxypyrrolooxazin 7-hydroxy analog; NMT 0.5 %	0.02 %	0.04 %	0.05 %	0.11 %	0.03 %	0.04%	0.14 %
Atorvastatin epoxy THF analog & Atorvastatin related Compound D; NMT 1.5 %	0.02 %	0.05 %	0.02 %	0.06 %	0.05 %	0.03%	0.09 %
Any other unspecified degradation product; NMT 0.2%	0.04 %	0.01 %	0.01 %	0.03 %	0.03 %	0.04%	0.06 %
Total impurities; NMT 4.0 %	0.20 %	0.30 %	0.23 %	0.52 %	0.26 %	0.22%	0.74 %
Ref. LNB	**R&D/0206, R&D/0211**						

Table 36: Stress Testing Results of Batch No.: 20-F-014-B (80 mg) Manufactured under Development Summary 04

Tests/Specifications	**Initial**	**Packaging Configuration:** 100CC HDPE container with 38mm CRC (without desiccant)					
		7 days	**7 days**	**7 days**	**14 days**	**14 days**	**14 days**
		40°C/75 %RH Open	**40°C/75 %RH Close**	**60°C Close**	**40°C/75 %RH Open**	**40°C/75 %RH Close**	**60°C Close**
Organic Impurities by HPLC							
Atorvastatin pyrrolidone analog; NMT 0.5%	0.05%	0.07%	0.06%	0.12%	0.07%	0.06%	0.15%
Atorvastatin related compound H; NMT 1.0%	0.04%	0.07%	0.05%	0.19%	0.03%	0.02%	0.27%
Atorvastatin epoxypyrrolooxazin 6-hydroxy analog; NMT 0.5%	0.02%	ND	ND	ND	ND	ND	ND
Atorvastatin epoxypyrrolooxazin 7-hydroxy analog; NMT 0.5%	0.02%	ND	0.03%	0.08%	0.03%	0.04%	0.07%
Atorvastatin epoxy THF analog & Atorvastatin related Compound D; NMT 1.5%	0.02%	0.05%	0.02%	0.07%	0.04%	0.03%	0.09%
Any other unspecified degradation product; NMT 0.2%	0.04%	0.01%	0.01%	0.02%	0.03%	0.04%	0.05%
Total impurities; NMT 4.0%	0.27%	0.21%	0.19%	0.51%	0.23%	0.23%	0.71%
Ref. LNB	**R&D/0206, R&D/0211**						

Inference:

Lactone impurity as well any other unknown impurity observed minimum at stress condition with selected formulation composition at formulation development summary 4. Hence, Batch No. 20-F-014 was selected for formulation and process optimization.

2.2.1.5 Formulation Optimization Study

Purpose:

The formulation optimization study was developed to establish the design space for formulation composition. Manufacturing process and formulation composition finalized in formulation development study 4 was considered basis for formulation optimization study.

Formulation optimization study of potential formulation components conducted independently for intra-granular part and extra-granular part. Considering the common granulation and common blending process for Atorvastatin Calcium Tablets, bracketing approach (80 mg and 10 mg) considered at formulation optimization stage, however, scale up batch has been evaluated for all strengths. Proposed optimization plan for the intra-granular formulation ingredient and extra-granular formulation ingredient has been presented in Table 37 and Table 38 respectively.

Table 37: Optimization Plan of Formulation Variables (Intra-granular)

Factors: Formulation Variables (Intragranular)	**Concentration of ingredient in optimization summary (% w/w to the core tablet)**		
	-1 (Lower concentration)	**0 (Optimum concentration)**	**+1 (Higher Concentration)**
Lactose Monohydrate (Pharmatose 200M)	8.478	23.478	38.478
Microcrystalline Cellulose (Vivapur 301)	23.241	38.241	53.241
Precipitated Calcium Carbonate (Sturcal L)	7.500	22.500	37.500
Sodium Starch Glycolate Type A (Primojel®)	1.500	2.500	3.500
Hydroxypropyl Cellulose (Klucel EF Pharm)	1.750	2.250	2.750

Table 38: Experimental Design for Intra-granular Formulation Optimization study

Design of Experiment		**Independent Variables (Intra-granular ingredient variation)**				
DOE Run No.	**Batch No.**	**Lactose Monohydrate (%)**	**Microcrystalline Cellulose (%)**	**Precipitated Calcium Carbonate (%)**	**Sodium Starch Glycolate (%)**	**Hydroxypropyl Cellulose (%)**
1	20G021	30.978	38.492	15.000	2.000	2.500
2	20G022	21.978	53.241	7.500	3.500	2.750
3	20G023	21.978	53.241	7.500	3.500	2.750
4	20G024	8.478	45.991	30.250	1.500	2.750
5	20G025	21.978	23.241	37.500	3.500	2.750
6	20G026	24.978	53.241	7.500	1.500	1.750
7	20G027	23.478	38.241	22.500	2.500	2.250
8	20G028	15.978	38.991	30.000	2.000	2.000
9	20G029	38.478	30.991	15.250	1.500	2.750
10	20G030	23.478	38.241	22.500	2.500	2.250
11	20G031	8.478	45.991	30.250	1.500	2.750
12	20G032	21.978	23.241	37.500	3.500	2.750
13	20G033	38.478	23.241	22.000	3.500	1.750
14	20G034	24.978	23.241	37.500	1.500	1.750
15	20G035	30.978	37.991	15.000	3.000	2.000
16	20G036	8.478	45.491	29.750	3.500	1.750
17	20G037	23.478	38.241	22.500	2.500	2.250

Table 39: Brief Manufacturing Procedure of the Batches for Intra-granular Optimization

Batch Size: 1.150 kg for each batch

Batch No.	Unit Operations	Specifications/Controls
20G021, 20G022, 20G023, 20G024, 20G025, 20G026, 20G027, 20G028, 20G029, 20G030, 20G031, 20G032, 20G033, 20G034, 20G035, 20G036, 20G037 (Common Blend)	Co-Sifting and Sifting	**Mesh used:** # 20 (Co-sift Atorvastatin calcium and Precipitated calcium carbonate) **Mesh used:** # 20 (Sift Microcrystalline Cellulose, Lactose Monohydrate and Sodium Starch Glycolate)
	Pre-mixing	**Equipment used:** Bin Blender **Bin used:** 5 L **Blender speed (RPM):** 10 **Mixing time:** 10 Min
	Top Spray Granulation	**Equipment used:** Fluid Bed Processor **Product container Used:** 8 L **Inlet air temperature:** 65 ± 10ºC **Solution pump speed (RPM):** 25± 5 **Product bed temperature:** 40 ± 10ºC **Atomizing air pressure (bar):** 1± 0.3
	Blending and Lubrication	**Equipment used:** Bin Blender **Mesh used for sifting of the extra-granular blending and lubricating materials:** # 40 **Bin used:** 5 L **Blender speed (RPM):** 10 **Blending Time:** 10 min (100 revolutions) **Lubrication Time:** 5 min (50 revolutions)
	Compression	**Equipment Used:** Tablet Compression Machine **Tooling:** 19.30 X 10.35 mm, Oval shape (80 mg), 9.80 X 5.10 mm, Oval shape (10 mg)
	Coating	**Equipment Used:** Gansons coater
Ref. LNB	**R&D/0154, R&D/0217, R&D/0221**	

Table 40: Physical Characterization of Different Batches of Intra-granular Optimization Stage (Granules)

Batch No.	Strength	Granules LOD at 105°C	Granules Bulk Density	Granules Tapped Density	Carr's Index	Hausner Ratio	Flow Character
20G021	80 mg and 10 mg	1.79%	0.43	0.46	6.52	1.07	Excellent
20G022		1.22%	0.44	0.45	2.22	1.02	Excellent
20G023		1.98%	0.35	0.39	10.26	1.11	Good
20G024		1.33%	0.43	0.56	23.21	1.30	Passable
20G025		1.46%	0.45	0.47	4.26	1.04	Excellent
20G026		1.42%	0.43	0.47	8.51	1.09	Excellent
20G027		1.84%	0.45	0.49	8.16	1.09	Excellent
20G028		1.94%	0.47	0.52	9.62	1.11	Excellent
20G029		1.62%	0.44	0.46	4.35	1.05	Excellent
20G030		1.29%	0.49	0.52	5.77	1.06	Excellent
20G031		1.94%	0.55	0.60	8.33	1.09	Excellent
20G032		1.82%	0.48	0.51	5.88	1.06	Excellent
20G033		1.59%	0.49	0.51	3.92	1.04	Excellent
20G034		1.26%	0.47	0.51	7.84	1.09	Excellent
20G035		1..86%	0.46	0.49	6.12	1.07	Excellent
20G036		1.87%	0.49	0.55	10.91	1.12	Good
20G037		1.65%	0.47	0.50	6.00	1.06	Excellent
Ref. LNB		**R&D/0217, R&D/0221**					

Table 41: Physical Characterization of Different Batches of Intra-granular Optimization Stage (Core Tablet)

Batch No.	**Strength**	**Uniformity of Weight (mg) Target: 1150.000 mg ± 5.0% (1092.500-1207.500) mg**			**Hardness (Kp)**			**Disintegration Time Target: NMT 15.0 minutes determined on 6 tablets (without disc)**		**Friability (%) (Target: NMT 1.0% w/w on NLT 6.50 g Tablets)**
		Min.	**Max.**	**Avg.**	**Min.**	**Max.**	**Avg.**	**FT**	**LT**	
20G021A	80 mg	1132.33	1164.12	1148.50	15.47	19.11	17.81	2'14"	2'20"	0.05%
20G022A		1146.77	1173.21	1161.49	22.14	24.84	23.68	1'44"	1'52"	0.02%
20G023A		1134.88	1167.18	1148.08	21.59	25.00	22.85	1'50"	3'20"	0.11%
20G024A		1139.54	1169.36	1153.53	16.86	19.70	18.33	2'10"	3'16"	0.03%
20G025A		1147.05	1169.94	1153.15	15.14	15.92	15.50	3'37"	4'04"	0.13%
20G026A		1145.15*	1167.80*	1154.75*	19.38	23.00	21.87	1'26"	1'40"	0.10%
20G027A		1145.82	1168.53	1153.84	16.82	19.43	18.16	1'52"	2'0"	0.06%
20G028A		1138.60	1175.57	1151.42	15.61	18.49	17.38	1'48"	1'54"	0.12%
20G029A		1137.12	1172.55	1155.49	17.79	21.18	19.35	2'24"	2'36"	0.09%
20G030A		1144.59	1157.93	1150.58	17.53	20.29	18.47	1'51"	2'0"	0.18%
20G031A		1145.24	1164.47	1156.89	17.53	19.43	18.44	1'31"	1'40"	0.10%
20G032A		1129.57	1172.58	1155.96	18.55	20.88	19.23	4'40"	4'52"	0.09%
20G033A		1139.9	1167.34	1155.02	14.79	18.49	16.65	2'36"	2'51"	0.17%
20G034A		1120.91	1187.49	1154.09	17.09	21.03	18.76	1'50"	1'54"	0.04%
20G035A		1128.98	1167.7	1149.98	17.36	20.39	18.91	1'34"	1'40"	0.07%
20G036A		1140.31	1176.15	1158.91	11.26	15.08	13.44	2'22"	2'40"	0.15%
20G037A		1140.07	1159.02	1152.25	17.86	19.92	18.93	1'40"	1'47"	0.05%
Ref. LNB		**R&D/0221**								

*Avg. weight calculated for 19 Tablet.

Table 42: Physical Characterization of Different Batches of Intra-granular Optimization Stage (Core Tablet)

Batch No.	Strength	Uniformity of Weight (mg) Target: 143.750 mg ± 5.0% (136.563-150.938) mg			Hardness (Kp)			Disintegration Time Target: NMT 15.0 minutes determined on 6 tablets (without disc)		Friability (%) (Target: NMT 1.0% w/w on NLT 6.50 g Tablets)
		Min.	Max.	Avg.	Min.	Max.	Avg.	FT	LT	
20G021B	10 mg	143.43	145.84	144.72	6.67	7.44	7.02	48"	52"	0.15%
20G022B		142.72	147.61	144.89	6.37	7.37	6.71	35"	46"	0.09%
20G023B		145.01	147.78	146.62	6.05	6.71	6.44	32"	43"	0.09%
20G024B		144.48	147.23	145.98	6.19	6.70	6.43	46"	51"	0.76%
20G025B		146.02	148.17	147.11	6.23	7.31	6.86	44"	55"	0.09%
20G026B		144.72	147.01	145.91	6.10	6.67	6.29	32"	38"	0.08%
20G027B		144.77	147.77	146.44	6.20	6.84	6.53	30"	36"	0.09%
20G028B		145.31	147.26	146.52	6.00	6.92	6.58	30'	37"	0.14%
20G029B		141.00	147.37	144.15	5.10	8.43	7.18	46"	52"	0.09%
20G030B		145.71	147.92	146.87	6.65	8.14	7.34	32"	37"	0.19%
20G031B		144.35	147.28	145.46	6.23	8.45	7.42	28"	32"	0.12%
20G032B		141.87	148.02	145.06	6.09	8.04	7.10	42"	45"	0.17%
20G033B		142.62	145.01	143.73	8.89	9.69	9.34	46"	51"	0.12%
20G034B		142.94	145.97	144.18	9.11	9.91	9.54	36"	42"	0.14%
20G035B		142.98	145.6	144.31	6.38	8.37	7.58	28"	31"	0.14%
20G036B		141.84	144.06	143.22	7.67	9.16	8.68	38"	42"	0.18%
20G037B		141.78	144.16	143.21	6.92	8.98	8.42	1'18"	1'26"	0.15%
Ref. LNB		**R&D/0221**								

Table 43: Dissolution Data of Generic Atorvastatin Calcium Tablets USP, 80 mg and 10 mg Tested under Formulation Optimization Studies (Intra-granular part) (Coated Tablet)

Dissolution Media	pH 6.8 Phosphate Buffer								
Apparatus	Paddle (USP Apparatus II)								
Volume	900 mL								
Speed	75 RPM								
% Drug Release in 30 min									
80 mg					**10 mg**				
Batch No.	**Avg.**	**Min.**	**Max.**	**% RSD**	**Batch No.**	**Avg.**	**Min.**	**Max.**	**% RSD**
20G021A	89	88	91	1.4	20G021B	90	88	91	1.4
20G022A	90	88	91	1.6	20G022B	91	89	92	1.5
20G023A	90	90	91	0.7	20G023B	92	90	93	1.3
20G024A	89	86	90	2.0	20G024B	89	88	90	0.7
20G025A	85	82	87	2.1	20G025B	89	88	89	0.6
20G026A	93	90	94	1.6	20G026B	93	91	94	0.9
20G027A	91	90	92	0.7	20G027B	90	89	91	0.7
20G028A	88	87	90	1.5	20G028B	90	88	91	1.6
20G029A	94	93	95	0.6	20G029B	92	89	95	2.3
20G030A	94	92	95	1.2	20G030B	94	93	95	0.9
20G031A	88	87	89	0.7	20G031B	90	88	93	2.3
20G032A	88	86	90	1.5	20G032B	92	91	93	1.0
20G033A	89	88	90	1.0	20G033B	89	88	89	0.4
20G034A	92	89	94	1.8	20G034B	90	89	91	0.8
20G035A	90	89	91	0.9	20G035B	92	90	94	1.8
20G036A	84	82	86	1.8	20G036B	81	77	85	3.4
20G037A	91	90	93	1.5	20G037B	89	88	90	0.8
Ref. LNB	**R&D/0209, R&D/0215**								

Table 44: Assay Result of Generic Atorvastatin Calcium Tablets USP, 80 mg and 10 mg Tested under Formulation Optimization Studies (Intra-granular part) (Coated Tablet)

80 mg		**10 mg**	
Batch No.	**% Assay (Limit: NLT 94.5 % and NMT 105.0% of the labeled amount of Atorvastatin)**	**Batch No.**	**% Assay (Limit: NLT 94.5 % and NMT 105.0% of the labeled amount of Atorvastatin)**
20G021A	98.8	20G021B	98.1
20G022A	97.8	20G022B	97.0
20G023A	100.0	20G023B	99.6
20G024A	100.9	20G024B	99.6
20G025A	100.3	20G025B	101.7
20G026A	99.2	20G026B	100.4
20G027A	98.8	20G027B	100.5
20G028A	97.1	20G028B	100.0
20G029A	98.1	20G029B	100.2
20G030A	98.9	20G030B	101.5
20G031A	100.9	20G031B	99.1
20G032A	100.0	20G032B	99.0
20G033A	99.7	20G033B	98.3
20G034A	99.6	20G034B	99.1
20G035A	98.8	20G035B	98.6
20G036A	99.8	20G036B	98.8
20G037A	99.1	20G037B	98.6
Ref. LNB	**R&D/0213, R&D/0211**		

Table 45: Content Uniformity Result of Generic Atorvastatin Calcium Tablets USP, 80 mg Tested under Formulation Optimization Studies (Intra-granular part) (Coated Tablet)

% of Atorvastatin Content									
Batch No.	**20G0021 A**	**20G0022 A**	**20G0023 A**	**20G024 A**	**20G025 A**	**20G026 A**	**20G027 A**	**20G028 A**	**20G029 A**
Sample 1	97.0	95.8	98.6	100.2	97.0	98.0	99.8	100.3	103.9
Sample 2	96.7	96.6	100.6	99.9	97.7	96.3	99.5	99.2	102.3
Sample 3	97.1	96.8	100.1	98.6	98.0	96.7	99.3	99.2	102.3
Sample 4	96.7	96.6	97.0	98.4	99.5	97.9	99.2	99.1	98.6
Sample 5	97.9	96.0	99.0	98.3	96.6	96.9	97.8	99.3	99.1
Sample 6	96.5	96.3	108.3	100.2	97.4	100.0	98.9	98.8	99.2
Sample 7	96.4	94.5	97.5	99.3	97.8	99.4	97.2	98.3	99.3
Sample 8	97.8	94.7	96.9	100.1	98.9	99.1	98.3	98.6	99.4
Sample 9	98.5	94.6	97.9	98.7	98.9	99.5	98.7	103.4	99.3
Sample 10	98.6	95.6	106.1	98.8	98.3	97.6	98.5	99.0	101.4
Average	97.3	95.7	100.2	99.3	98.0	98.1	98.7	99.5	100.5
Minimum	96.4	94.5	96.9	98.3	96.6	96.3	97.2	98.3	98.6
Maximum	98.6	96.8	108.3	100.2	99.5	100.0	99.8	103.4	103.9
%RSD	0.8	0.9	3.9	0.8	0.9	1.3	0.8	1.5	1.8
Acceptance value ≤15	3.1	4.9	9.5	1.9	2.7	3.5	1.9	3.5	4.4
Ref. LNB	**R&D/0211, R&D/0212, R&D/0203, R&D/0213**								

Table 46: Content Uniformity Result of Generic Atorvastatin Calcium Tablets USP, 80 mg Tested under Formulation Optimization Studies (Intra-granular part) (Coated Tablet)

% of Atorvastatin Content								
Batch No.	**20G0030 A**	**20G0031 A**	**20G0032 A**	**20G033 A**	**20G034 A**	**20G035 A**	**20G036 A**	**20G037 A**
Sample 1	99.1	101.5	97.5	99.9	98.0	101.9	102.6	101.0
Sample 2	101.8	102.9	99.3	97.8	97.0	103.0	105.2	102.6
Sample 3	99.6	105.2	98.1	97.8	96.7	101.4	103.0	103.0
Sample 4	99.5	104.2	101.2	98.0	97.6	103.5	103.3	101.5
Sample 5	100.3	102.5	97.8	98.5	100.4	103.4	104.7	101.7
Sample 6	99.5	103.5	100.3	98.2	99.7	101.7	101.5	101.3
Sample 7	100.7	101.3	98.7	99.9	98.2	102.9	102.7	102.4
Sample 8	99.0	104.8	100.1	97.1	98.9	100.8	103.1	102.8
Sample 9	101.5	102.8	100.5	99.1	100.4	102.4	101.2	103.2
Sample 10	98.8	105.7	98.7	98.8	101.3	101.2	103.2	102.4
Average	100.0	103.4	99.2	98.5	98.8	102.2	103.1	102.2
Minimum	98.8	101.3	97.5	97.1	96.7	100.8	101.2	101.0
Maximum	101.8	105.7	101.2	99.9	101.3	103.5	105.2	103.2
%RSD	1.1	1.5	1.3	0.9	1.6	0.9	1.2	0.7
Acceptance value ≤15	2.5	5.5	3.1	2.2	3.7	3.0	4.5	2.4
Ref. LNB	**R&D/0211, R&D/0212, R&D/0203, R&D/0213**							

Table 47: Content Uniformity Result of Generic Atorvastatin Calcium Tablets USP, 10 mg Tested under Formulation Optimization Studies (Intra-granular part) (Coated Tablet)

% of Atorvastatin Content									
Batch No.	**20G0021 B**	**20G0022 B**	**20G0023 B**	**20G024 B**	**20G025 B**	**20G026 B**	**20G027 B**	**20G028 B**	**20G029 B**
Sample 1	95.3	94.4	96.2	103.0	102.7	100.6	99.0	100.2	100.0
Sample 2	96.8	93.3	96.0	101.9	102.0	102.2	100.0	101.7	102.3
Sample 3	95.2	93.0	95.4	101.6	101.4	100.2	98.8	100.5	103.1
Sample 4	96.1	94.3	97.7	102.2	101.2	99.1	102.1	99.8	100.1
Sample 5	95.0	94.0	97.5	102.9	104.1	101.5	101.9	100.4	101.4
Sample 6	95.7	95.4	97.0	105.5	100.5	100.7	102.3	99.6	103.1
Sample 7	98.8	94.7	95.3	105.3	100.4	99.0	99.3	100.7	104.2
Sample 8	96.9	93.9	96.7	103.0	100.2	100.9	99.7	102.0	100.2
Sample 9	96.1	94.4	96.2	104.7	100.7	101.0	101.1	100.2	100.1
Sample 10	98.2	94.2	98.0	103.5	102.9	101.5	99.5	101.8	101.6
Average	96.4	94.2	96.6	103.4	101.6	100.7	100.4	100.7	101.6
Minimum	95.0	93.0	95.3	101.6	100.2	99.0	98.8	99.6	100.0
Maximum	98.8	95.4	98.0	105.5	104.1	102.2	102.3	102.0	104.2
%RSD	1.3	0.7	1.0	1.4	1.3	1.0	1.4	0.8	1.5
Acceptance value ≤15	5.1	6.0	4.2	5.2	3.2	2.4	3.3	2.1	3.7
Ref. LNB	**R&D/ 0211, R&D/ 0212, R&D/ 0203, R&D/ 0213**								

Table 48: Content Uniformity Result of Generic Atorvastatin Calcium Tablets USP, 10 mg Tested under Formulation Optimization Studies (Intra-granular part) (Coated Tablet)

% of Atorvastatin Content								
Batch No.	**20G0030 B**	**20G0031 B**	**20G0032 B**	**20G033 B**	**20G034 B**	**20G035 B**	**20G036 B**	**20G037 B**
Strength	**10 mg**	**10 mg**	**10 mg**	**10 mg**	**10 mg**	**10 mg**	**10 mg**	**10 mg**
Sample 1	98.2	94.2	94.9	95.3	94.1	94.8	96.1	95.7
Sample 2	97.4	100.1	98.7	94.5	96.6	94.2	96.2	93.4
Sample 3	98.1	96.5	98.6	95.2	96.8	93.6	95.1	95.1
Sample 4	98.6	95.0	99.6	95.4	98.0	96.0	96.0	95.9
Sample 5	92.8	99.7	98.1	95.0	99.4	93.5	94.3	97.6
Sample 6	99.5	102.3	96.8	97.3	95.4	96.1	95.3	93.1
Sample 7	98.5	95.0	99.1	97.0	96.5	96.8	95.7	93.5
Sample 8	99.7	97.7	95.8	96.1	97.0	96.7	94.3	91.8
Sample 9	98.2	96.7	97.9	93.9	95.2	97.1	93.2	96.3
Sample 10	97.0	95.2	98.1	95.9	94.6	93.6	93.8	95.0
Average	97.8	97.2	97.8	95.6	96.4	95.2	95.0	94.7
Minimum	92.8	94.2	94.9	93.9	94.1	93.5	93.2	91.8
Maximum	99.7	102.3	99.6	97.3	99.4	97.1	96.2	97.6
%RSD	0.8	2.8	1.4	1.1	1.7	1.5	1.1	1.8
Acceptance value ≤15	2.1	7.7	3.9	5.4	6.0	6.8	6.0	8.0
Ref. LNB	**R&D/ 0211, R&D/ 0212, R&D/ 0203, R&D/ 0213**							

Table 49: Design Range of Formulation Variables (Intra-granular part) for Generic Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg

Factors: Formulation Variables (Intra-granular)	% w/w amount in Final Formulation (Core Tablet)	Design Space in Formulation (% w/w to the core tablet)
Lactose Monohydrate (Pharmatose 200M)	23.478	(8.478-38.478)
Microcrystalline Cellulose (Vivapur 301)	38.241	(23.241-53.241)
Precipitated Calcium Carbonate (Sturcal L)	22.500	(7.500-37.500)
Sodium Starch Glycolate Type A (Primojel®)	2.500	(1.500-3.500)
Hydroxypropyl Cellulose (Klucel EF Pharm)	2.250	(1.750-2.750)

Extra-granular Formulation Component Optimization

Table 50: Optimization Plan of Extra-granular Formulation Components

Factors: Formulation Variables (Extra-granular)	Concentration of ingredient in Optimization summary (% w/w to the core tablet)		
	-1 (Lower concentration)	0 (Optimum concentration)	+1 (Higher Concentration)
Croscarmellose Sodium (%)	2.100	2.750	2.900
Magnesium Stearate (%)	0.350	0.750	1.150

Table 51: Experimental Design for Extra-granular Optimization Study

Design of Experiment		Independent Variables (Extra-granular)	
DOE Run No.	Batch No.	Croscarmellose Sodium (%)	Magnesium Stearate (%)
1	20G045A	2.100	1.150
2	20G045B	2.900	0.350
3	20G045C	2.500	0.750
4	20G045D	2.500	0.750
5	20G045E	2.300	0.950
6	20G045F	2.700	0.550

Table 52: Brief Manufacturing Procedure of Different Extra-granular Formulation Optimization Batches

Batch Size: 6.289 kg (Further divided into 6 sub batches; Batch No. 20G045A, 20G045B, 20G045C, 20G045D, 20G045E and 20G045F for Extra-granular Optimization)

Batch No.	Unit Operations	Specifications/Controls
20G045 (Common Blend)	Co-Sifting and Sifting	**Equipment used:** Vibratory Sifter **Mesh used:** # 20 (Co-sift Atorvastatin calcium and Precipitated calcium carbonate) **Mesh used:** # 20 (Sift Microcrystalline Cellulose, Lactose Monohydrate and Sodium Starch Glycolate)
	Pre-mixing	**Equipment used:** Bin Blender **Bin used:** 40 L **Blender speed (RPM):** 10 **Mixing time:** 10 min (100 revolutions)
	Top Spray Granulation	**Equipment used:** Fluid Bed Processor **Product container used:** 40 L **Inlet air temperature:** 65 ± 10ºC **Solution pump speed (RPM):** 30± 5 **Product bed temperature:** 40 ± 10ºC **Atomizing air pressure (bar):** 1± 0.3
	Blending and Lubrication	**Equipment used:** Bin Blender **Mesh used for sifting of the extra-granular blending and lubricating materials:** # 40 **Bin used:** 5 L **Blender speed (RPM):** 10 **Blending Time:** 10 min (100 revolutions) **Lubrication Time:** 5 min (50 revolutions)
	Compression	**Equipment Used:** Tablet Compression Machine **Tooling:** 19.30 X 10.35 mm, Oval shape (80 mg), 9.80 X 5.10 mm, Oval shape (10 mg)
	Coating	**Equipment Used:** Gansons coater **Coating pan used:** 273mm
Ref. LNB	**R&D/0154, R&D/0221**	

Table 53: Physical Characterization of Different Batches of Extra-granular Optimization Stage (Core tablet)

Batch No.	**Strength**	**Uniformity of Weight (mg) Target: 1150.000 mg ± 5.0% (1092.500-1207.500) mg**			**Hardness (Kp)**			**Disintegration Time Target: NMT 15.0 minutes determined on 6 tablets (without disc)**		**Friability (%) (Target: NMT 1.0% w/w on NLT 6.50 g Tablets)**
		Min.	**Max.**	**Avg.**	**Min.**	**Max.**	**Avg.**	**FT**	**LT**	
20G045A1	80 mg	1136.10	1157.08	1142.79	15.21	17.22	16.36	2'00"	2'06"	0.10%
20G045B1		1143.26	1161.71	1153.56	16.82	19.65	18.54	2'06"	2'09"	0.02%
20G045C1		1135.12	1163.52	1149.54	17.95	20.42	19.03	2'12"	2'24"	0.02%
20G045D1		1135.46	1167.18	1153.17	19.03	22.75	21.49	2'08"	2'12"	0.02%
20G045E1		1140.99	1170.44	1154.63	20.84	23.50	21.95	2'06"	2'09"	0.05%
20G045F1		1131.22	1160.77	1151.45	17.51	21.22	19.77	2'00"	2'07"	0.04%
Ref. LNB		**R&D/0221**								

Table 54: Dissolution Data for Generic Atorvastatin Calcium Tablets USP, 80 mg and 10 mg Tested under Formulation Optimization Studies (Extra-granular part) (Coated tablet)

Dissolution Media	pH 6.8 Phosphate Buffer								
Apparatus	Paddle (USP Apparatus II)								
Volume	900 mL								
Speed	75 RPM								
% Drug Release in 30 min									
80 mg					**10 mg**				
Batch No.	**Avg.**	**Min.**	**Max.**	**% RSD**	**Batch No.**	**Avg.**	**Min.**	**Max.**	**% RSD**
20G045A1	89	87	90	1.2	20G045A2	90	89	92	1.3
20G045B1	86	85	88	1.4	20G045B2	89	86	90	1.5
20G045C1	87	85	89	1.4	20G045C2	91	90	93	1.2
20G045D1	88	86	89	1.1	20G045D2	92	91	92	0.6
20G045E1	89	86	90	1.5	20G045E2	93	92	94	0.6
20G045F1	89	87	90	1.5	20G045F2	93	91	95	1.3
Ref. LNB	**R&D/0209, R&D/0215**								

Table 55: Assay Result of Generic Atorvastatin Calcium Tablets USP, 80 mg and 10 mg Tested under Formulation Optimization Studies (Extra-granular part) (Coated tablet)

80 mg		**10 mg**	
Batch No.	**% Assay (Limit: NLT 94.5 % and NMT 105.0% of the labeled amount of Atorvastatin)**	**Batch No.**	**% Assay (Limit: NLT 94.5 % and NMT 105.0% of the labeled amount of Atorvastatin)**
20G045A1	95.8	20G045A2	98.8
20G045B1	98.0	20G045B2	98.8
20G045C1	98.3	20G045C2	101.5
20G045D1	97.6	20G045D2	101.4
20G045E1	97.1	20G045E2	101.4
20G045F1	100.4	20G045F2	99.6
Ref. LNB	**R&D/0203**		

Hence, concentration range considered in extra-granular formulation optimization study will be design space for respective ingredients in the formulation presented in Table 56.

Table 56: Design Range of Formulation Variables (Extra-granular part) for Generic Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg

Formulation Variables (Extra-granular)	**% w/w amount in Final Formulation (Core Tablet)**	**Design Space in Formulation (% w/w to the core tablet)**
Croscarmellose Sodium	2.750%	(2.100-2.900) %
Magnesium Stearate	0.750%	(0.350-1.150) %

Based on formulation optimization study, it can be concluded that finalized composition presented in table 57 is suitable for process optimization summary and scale up.

Table 57: Final composition studied in formulation optimization study

S/N	**Ingredients**	**Amount (mg / Tablet)**				**(% w/w to the core tablet)**
		80 mg	**40 mg**	**20 mg**	**10 mg**	
Intra-granular						
1	Atorvastatin Calcium Trihydrate USP*	86.6000	43.3000	21.6500	10.8250	7.241
2	Precipitated Calcium Carbonate (Sturcal L)	258.7500	129.3750	64.6875	32.3438	21.635
3	Microcrystalline Cellulose (Vivapur 301)	439.7750	219.8875	109.9437	54.9719	36.770
4	Lactose Monohydrate (Pharmatose 200M)	270.0000	135.0000	67.5000	33.750	22.575
5	Sodium Starch Glycolate Type A (Primojel®)	28.7500	14.3750	7.1875	3.5938	2.404
Binder Solution						
6	Hydroxy Propyl Cellulose (Klucel EF Pharm)	25.8750	12.9375	6.4688	3.2344	2.163
7	Polysorbate 80 (Kolliphor PS 80)	2.8750	1.4375	0.7188	0.3594	0.240
8	Purified Water@	QS	QS	QS	QS	N/A
Extra-granular						
9	Croscarmellose Sodium (Ac-Di-Sol® SD-711)	28.7500	14.3750	7.1875	3.5938	2.404
10	Magnesium Stearate (Veg.)	8.6250	4.3125	2.1563	1.0781	0.721
Total weight of core tablet (mg)		**1150.000**	**575.000**	**287.500**	**143.750**	N/A

S/N	Ingredients	Amount (mg/ Tablet)				(% w/w to the core tablet)
		80 mg	40 mg	20 mg	10 mg	
Film Coating						
11	Opadry II Complete Film Coating System (White; 85F18422)	40.2500	20.1250	10.0625	5.0313	3.365
12	Hypromellose 2910, 6 mPa.s	2.8750	1.4375	0.7188	0.3594	0.240
13	Opadry® Complete Film Coating System ((Clear; YS-1R-7006)	2.8750	1.4375	0.7188	0.3594	0.240
14	Purified Water@	QS	QS	QS	QS	N/A
Total weight of coated tablet (mg)		**1196.000**	**598.000**	**299.000**	**149.499**	**100.000**

*Equivalent to 10 mg, 20 mg, 40 mg and 80 mg of Atorvastatin; @ Purified water evaporate during drying process and not a part of final product.

2.2.1.6 Updated Risk Assessment of the Formulation Variables

During formulation development, the high risks for each component of the overall drug product formulation were addressed. Experimental studies were defined and executed to develop additional scientific knowledge and understanding and to reduce the risk to an acceptable level. After detailed experimentation, the initial overall risk assessment of the formulation components was updated in-line with the current product understanding. Table 58 and 59 provide the updated risk assessment of the formulation and the justification for the reduced risk following formulation development respectively.

Table 58: Updated Risk Assessment of Formulation Variables on Drug Product CQAs

Drug product CQAs	**Formulation Variables**							
	Drug Substance PSD	**Calcium carbonate amount**	**Diluent type & level**	**Disintegrant type & level**	**Binder type & level**	**Surfactant type & level**	**Lubricant type & level**	**Coating materials type and level**
Assay	Low*	Low*	Low*	Low	Low	Low	Low	Low
Content uniformity	Low*	Low*	Low*	Low	Low	Low	Low	Low
Dissolution	Low*	Low*	Low*	Low*	Low*	Low*	Low*	Low*
Degradation Products	Low	Low*	Low	Low*	Low	Low*	Low	Low*

***The level of risk is reduced to Low from initial risk assessment**

Table 59: Justification of the Reduced Risk of Formulation Attributes on Drug Product CQAs

API Attributes	**Drug Products CQAs**	**Risk Category**	**Justification**
Drug Substance PSD	Assay	Low	The poor flow of the drug substance is mitigated by adopting top spray granulation process with combination of three diluents [Microcrystalline Cellulose (301), Lactose Monohydrate (200M) and Precipitated Calcium Carbonate (Sturcal L)]. Acceptable assay and content uniformity obtained with the selected composition and manufacturing process. The risk is reduced to **Low.**
	Content uniformity	Low	
	Dissolution	Low	Acceptable dissolution (> 85% in 30 min) is obtained with the selected drug substance PSD (D_{90} not more than 50 µm) as well as top spray granulation technique. The risk is reduced to **Low.**
Calcium carbonate amount	Assay	Low	Calcium carbonate is compatible with atorvastatin calcium and maintain alkaline pH in the dosage form. During formulation optimization of intra-granular part, calcium carbonate percentage in formulation has been optimized. Acceptable assay, content uniformity, dissolution and degradation products obtained with finalized composition and manufacturing process with optimized amount of calcium carbonate. The risk is reduced to **Low.**
	Content uniformity	Low	
	Dissolution	Low	
	Degradation Products	Low	
Diluent type & level	Assay	Low	The poor flow of the drug substance is mitigated by adopting top spray granulation process with combination of three diluents. [Microcrystalline Cellulose (301), Lactose Monohydrate (200M) and

API Attributes	**Drug Products CQAs**	**Risk Category**	**Justification**
	Content uniformity	Low	Precipitated Calcium Carbonate (Sturcal L)]. Acceptable assay and content uniformity obtained with the selected composition and manufacturing process. The risk is reduced to **Low.**
	Dissolution	Low	Level of diluent can impact tablet dissolution via tablet hardness. However, batches with selected diluent [Microcrystalline Cellulose (301), Lactose Monohydrate (200M) and Precipitated Calcium Carbonate (Sturcal L)] and standard hardness range meet predefined dissolution criteria (> 85% in 30 min). The risk is reduced to **Low.**
Disintegrant type & level	Dissolution	Low	Disintegrant type and Level have impact on tablet disintegration and dissolution. However, Optimized level of sodium starch glycolate type A at intra-granular part and croscarmellose sodium at extra granular part provided acceptable dissolution for all batches manufactured in formulation optimization studies. Effect of acidic nature of disintegrant on degradation product generation in dosage form masked by use of calcium carbonate. The risk is reduced to **Low.**
	Degradation Products	Low	
Binder type & level	Dissolution	Low	Level of hydroxypropyl cellulose (Klucel EF) in final formulation meet predefined dissolution criteria (> 85% in 30 min). The risk is **Low**.
Surfactant type & level	Dissolution	Low	Atorvastatin Calcium is a BCS class II molecule and level of polysorbate 80 in final formulation meet predefined dissolution criteria (> 85% in 30 min). Polysorbate 80 found compatible in dosage form in presence of calcium carbonate. The risk is reduced to **Low.**
	Degradation Products	Low	
Lubricant type & level	Dissolution	Low	Drug product showed good stability at prototype stability study with the Magnesium stearate level selected in final formulation. The risk is reduced to **Low**.
Coating Materials type and level	Dissolution	Low	Type and level of coating materials have impact on tablet disintegration and dissolution. However, level of coating materials in final formulation meet predefined dissolution criteria (> 85% in 30 min). The risk is reduced to **Low.**
	Degradation Products	Low	Stability data of prototype batch demonstrated good physicochemical stability with selected coating composition. The risk is reduced to **Low.**

2.2.2 Overages

There are no overages used in the formulation of Generic Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg.

2.2.3 Manufacturing Process Development

Wet granulation process was chosen as an appropriate manufacturing process and required equipment was selected for generic Atorvastatin Calcium Tablets USP. Each process step in the manufacturing process is listed in the sequence of occurrence. It also includes the input material attributes and process parameters that can potentially impact intermediate and finished product quality attributes. The material attributes of the input materials and the process parameters used at the very first process step determine the quality attributes of the output material (intermediate) produced at this step. Material attributes of the intermediate from this step and process parameters of the subsequent process step in the manufacturing process will determine quality attributes of the next intermediate and, eventually, those of the finished drug product. This cycle repeats until the final process step where finished drug product is manufactured and the product quality attributes are evaluated. This map was used to guide the risk assessments performed during process development. Note that this process map excludes the quantities of raw materials (i.e. diluent/binder, glidant/solubilizer, disintegrant, lubricant and coating materials) from the material attributes column because these are evaluated as part of formulation development. Figure 7 presents the process map for the finalized formulation of Atorvastatin Calcium Tablets USP.

Processing parameters	Input material's attributes	Manufacturing processing Steps	Quality of output material's attributes
Screen type & size	API PSD & Flow ability Excipients PSD & Flow ability Excipients bulk & tapped density Moisture content	**Sifting**	Powder PSD Powder Flow ability Powder bulk density
Inlet air volume Inlet air RH (%) Inlet air temperature Product bed temperature Shaking interval	Granules uniformity Moisture content	**Top Spray Granulation (FBP)**	Granules uniformity Granules bulk density and flow property Granules LOD
Screen size Machine speed Sieve size	Granules uniformity Granules bulk density and flow property Granules LOD	**Size Reduction**	Granules flow ability & bulk density Granule size distribution
Order of Addition Blender Type/ Geometry No. of revolutions (time and speed) Capacity utilized	Extra granular excipients type/grade; Surface area of Magnesium Stearate Granules flow ability & bulk density Granule size distribution	**Blending and Lubrication**	Final Blend Blend uniformity PSD Bulk density Flow ability; Compressibility
Pre-compression force Main compression force Press speed Feeder speed/Type	Blend uniformity Blend PSD Bulk density Flow ability/Compressibility/Compact ability	**Compression**	Compressed Tablets Assay Content uniformity Disintegration/Dissolution Weight Variation Hardness Friability
Inlet air volume Inlet air temperature Inlet air RH (%) Product bed temperature Atomizing air pressure Bed to gun distance Solid content of coating solution; Dew point; Pan speed; Final drying	Appearance Weight variation Hardness Impurity Moisture content Film coating agent type Solid content of coating agent Solvent type	**Coating**	Appearance Process efficiency Weight variation Hardness Impurity Water content
Torque speed Tablet counter Line speed Induction seal	Container and closure type & size	**Packaging**	Chemical stability, Product Appearance

Figure 7: Process Map for Generic Atorvastatin Calcium Tablets USP.

2.2.3.1 Initial Risk Assessment of the Drug Product Manufacturing Process

A risk assessment of the overall drug product manufacturing process was performed to identify the high risk steps that may affect the CQAs of the final drug product. Subsequently, the CQAs of the output material from each process step that impact the final drug product CQAs was identified. For each process step, a risk assessment was conducted to identify potentially high risk process variables which could impact the identified intermediate CQAs and, ultimately, the drug product CQAs. These variables are then investigated in order to have better understanding of the manufacturing process and to develop a control strategy to reduce the risk factor. This method of identifying process variables for further summary is illustrated in Figure 8 and is applied in each process step risk assessment.

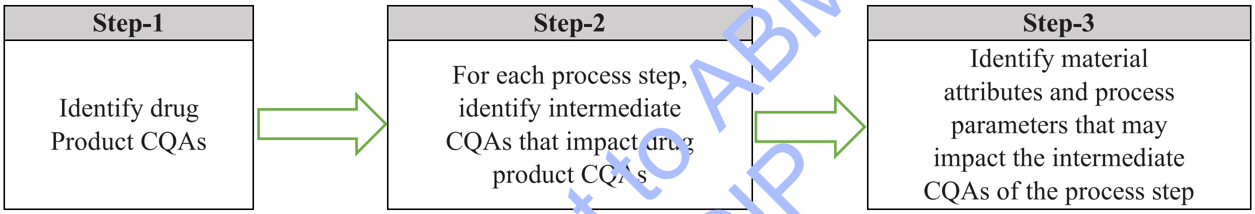
Step-1
Identify drug Product CQAs
Step-2
For each process step, identify intermediate CQAs that impact drug product CQAs
Step-3
Identify material attributes and process parameters that may impact the intermediate CQAs of the process step

Figure 8: Schematic of the method used to identify process variables for further summary.

The initial risk assessment of the overall manufacturing process is shown in Table 60. Justification for each risk assessment is presented in Table 61.

Table 60: Initial Risk Assessment of the Manufacturing Process on Drug Product CQAs

Drug product CQAs	**Manufacturing Process Steps**						
	Co-Sifting & Sifting	**Pre-Mixing**	**Top Spray Granulation and Size Reduction**	**Blending and Lubrication**	**Compression**	**Coating**	**Packaging**
Assay	Medium	Medium	High	Medium	Medium	Low	Low
Content uniformity	Medium	Medium	High	High	High	Low	Low
Dissolution	Low	Low	High	High	High	Medium	Low
Degradation Products	Medium	Low	Low	Low	Low	High	Medium

Table 61: Justification of Initial Risk Assessment of Manufacturing Unit Operations on Drug Product CQAs.

Process Steps	**Drug Product CQAs**	**Risk Category**	**Justification**
Co-sifting & sifting	Assay	Medium	Drug substance concentration is around 7.3% w/w in the drug product and exhibits very poor flow property. That's why, co-sifting and sifting step may impact on assay and content uniformity. Therefore, the risk is **Medium.**
	Content uniformity	Medium	
	Dissolution	Low	Co-sifting & Sifting stage are unlikely to affect dissolution. The risk is **Low.**
	Degradation Products	Medium	As atorvastatin calcium is sensitive to acid and oxidative degradation, therefore degradation product may be generated in contact with the excipient having acidic surface and oxidative residue. That's why, co-sifting and sifting step may impact on degradation product generation. Hence, the risk is **Medium.**
Pre-Mixing	Assay	Medium	Drug substance concentration is around 7.3% w/w in the drug product and exhibits very poor flow property. Pre mixing step may influence uniformity of drug distribution at granulation stage and ultimately on assay and content uniformity. However, top spray granulation. helps to fix the API particle within the granulation and thus prevents segregation during processing. Therefore, the risk is **medium**.
	Content uniformity	Medium	
	Dissolution	Low	Pre-mixing stage are unlikely to impact on dissolution and degradation product of the co sifted materials. The risk is **Low.**
	Degradation Products	Low	
Top Spray Granulatio	Assay	High	Drug substance concentration is around 7.3% w/w in the drug product and exhibits very poor flow property. Potential process
	Content uniformity	High	

n and Size Reduction	Dissolution	High	parameters at top spray granulation and size reduction stage may impact the granules uniformity which may impact on assay, content uniformity and dissolution. The risk is **High.**
	Degradation Products	Low	Atorvastatin calcium is stable at wet granulation process and satisfactory physicochemical stability found for the finalized formulation. Therefore, the risk is **Low.**
Blending and Lubrication	Assay	Medium	The granule uniformity is controlled by earlier steps. In this step granules blend with some extra granular excipients. Therefore, the risk is **Medium**.
	Content uniformity	High	Though the granule uniformity is controlled by earlier steps, over lubrication can impact the content uniformity for the low API content (around 7.3% w/w) drug product due breakdown of the top spray granules. Therefore, the risk is **High**.
	Dissolution	High	Over-lubrication due to an excessive number of revolutions may impact disintegration and dissolution of the tablets for BCS class II compound. The risk is **High.**
	Degradation Products	Low	Lubrication is unlikely to impact degradation products; Therefore, the risk is **Low.**
Compression	Assay	Medium	In extreme cases tablet weight variability in compression stage can lead out of specification assay result. Hence, the risk is **Medium**.
	Content uniformity	High	Compression process variables can cause tablet weight variability which could cause tablets to fall out-of-specification for content uniformity. Due to low API content (around 7.3% w/w) in the drug product, the risk is **High.**
	Dissolution	High	Compression process variables may impact disintegration and ultimately, dissolution of the tablets. The risk is **High.**
	Degradation Products	Low	Compression force is unlikely to impact degradation products. The risk is **Low.**
Coating	Assay	Low	Coating is unlikely to impact assay and content uniformity. The risk is **Low.**
	Content uniformity	Low	
	Dissolution	Medium	High weight gain can increase the disintegration time of the tablets which can impact the dissolution. However, water soluble film coating agents intended to use for film coating. The risk is **Medium.**
	Degradation Products	High	Coating process variables impact the weight gain and coating uniformity at film coating stage which can affect the degradation product generation; therefore, the risk is **High.**
Packaging	Assay	Low	Packaging is unlikely to impact assay, content uniformity and dissolution. The risk is **Low.**
	Content uniformity	Low	
	Dissolution	Low	
	Degradation Products	Medium	Around 4.0% weight gain considered at film coating stage and prototype formulation stability at HDPE container and closure

			system along with desiccator showed good stability. The risk is **Medium**

Further risk assessment was performed subsequently on each process step to identify which process variables may potentially impact the intermediate CQAs. Evaluation of all possible process variables that could potentially impact the quality attributes of the output material of any given process step is not feasible; therefore, few of the variables are set constant based on current understanding.

2.2.3.2 Top Spray Granulation (FBP) and Size Reduction Stage Optimization

Based on knowledge of formulation development studies, initial risk assessment of the top spray granulation process variables has been provided in Table 62. Inlet air temp, Atomizing air pressure and dosing RPM are identified as most potentially critical process parameters for further evaluation to establish limits for these CPPs (and CMAs) within which the quality of drug product will be assured. Justification for each risk assessment is presented in Table 63. Additional parameters were set/considered at their optimum fixed constant level in order to reduce uncontrolled noise and variability.

Table 62: Initial Risk Assessment of the Top Spray Granulation (FBP) Stage Variables on Output Materials CQAs

Output material CQA	**Top Spray Granulation Process Variables**				**Size Reduction Stage Variables**	
	Inlet Temperature (°C)	**Inlet Air Volume (CFM)**	**Peristaltic Pump (RPM)**	**Atomizing Air Pressure (Bar)**	**Size reduction equipment**	**Mesh size/Screen Size**
Granules size distribution	Medium	Medium	Medium	High	Medium	Medium
Granules bulk density	Low	Medium	High	High	Medium	Medium
Granules LOD	High	Medium	Medium	Low	Low	Low
Dissolution	Low	Low	Low	Low	Low	Low
Degradation Products	Medium	Low	Low	Low	Low	Low

Table 63: Justification of Initial Risk Assessment of Fluid Bed Drying and Size Reduction Stage Variables on Output materials CQAs

Input Material Attributes	Drug Products CQAs	Risk Category	Justification
Inlet Temperature (º C)	Granules size distribution	Medium	Aqueous granulation process requires high inlet air temperature. High inlet air temperature than optimum will spray dry granulating liquid solution before it can effective form bridges between primary particles. If the inlet air temperature is too low, it will generate lump formation. Therefore, the risk is **Medium.**
	Granules bulk density	Low	Higher or lower inlet air temperature has no impact on granules growth. The risk is **Low.**
	Granules LOD	High	Higher or lower inlet air temperature has impact on granules LOD. The risk is **High.**
	Dissolution	Low	Inlet air temperature have no impact on tablet dissolution. The risk is **Low.**
	Degradation Products	Medium	Uncontrolled drying can destabilize the drug product and water content present in the Atorvastatin calcium is necessary to maintain in drug product for stabilization. The risk is **Medium.**
Inlet Air Volume (CFM)	Granules size distribution	Medium	Optimum air flow needed to fluidize the bed without clogging the filters during granulation. Higher air flow will cause attrition and rapid evaporation, generating smaller granules and fines. However, atomizing air pressure and size reduction stage has profound impact on final granules size. Therefore, the risk is **Medium.**
	Granules bulk density	Medium	Higher or lower air flow can impact on granules size distribution which can impact the bulk density. However, atomizing air pressure and size reduction stage has profound impact on granule bulk density. Therefore, the risk is **Medium.**
	Granules LOD	Medium	Granules LOD is impacted by inlet air flow. Optimum air flow is needed to fluidize the bed without clogging the filters. The risk is **Medium.**
	Dissolution	Low	Fluidizing air volume (CFM) unlikely to impact dissolution and degradation products. The risk is **Low.**
	Degradation Products	Low	
Peristaltic Pump Speed (RPM)	Granules size distribution	Medium	Peristaltic Pump Speed (RPM) can impact the drying time consequently granule size distribution and LOD. Therefore, the risk is **Medium.**
	Granules LOD	Medium	

Input Material Attributes	Drug Products CQAs	Risk Category	Justification
	Granules bulk density	High	Peristaltic Pump Speed (RPM) have impact on bigger and dense granules formation. The risk is **High.**
	Dissolution	Low	At optimized atomization, peristaltic pump speed (RPM) is unlikely to impact dissolution and degradation products. The risk is **Low.**
	Degradation Products	Low	
Atomizing Air Pressure (Bar)	Granules size distribution	High	Granules size distribution and bulk density is impacted by lower or higher atomizing air pressure. The risk is **High.**
	Granules bulk density	High	
	Granules LOD	Low	Atomizing air pressure is unlikely to impact granules LOD, dissolution and degradation products. The risk is **Low.**
	Dissolution	Low	
	Degradation Products	Low	
Size reduction equipment	Granules size distribution	Medium	The breakage of particles due to intense shear applied between particle and size reduction equipment ultimately impact on granules size distribution. Therefore, the risk is **Medium.**
	Granules bulk density	Medium	Granules bulk density is correlated to granules size which is impacted by size reduction equipment. The risk is **Medium.**
	Granules LOD	Low	Size reduction equipment unlikely to impact granules LOD, dissolution and degradation products. The risk is **Low.**
	Dissolution	Low	
	Degradation Products	Low	
Mesh size/Screen Size	Granules size distribution	Medium	Granules size distribution and bulk density is impacted by mesh size/screen size. The risk is **Medium.**
	Granules bulk density	Medium	
	Granules LOD	Low	Mesh size/Screen size in milling process unlikely to impact granules LOD, dissolution and degradation products. The risk is **Low.**
	Dissolution	Low	
	Degradation Products	Low	

Table 64: Manufacturing Formula for Process Optimization Summary (Top Spray Granulation)

S/N	Ingredients	Amount (mg/ Tablet)				(% w/w to the core tablet)
		80 mg	40 mg	20 mg	10 mg	
Intra-granular						
1	Atorvastatin Calcium Trihydrate USP*	86.6000	43.3000	21.6500	10.8250	7.241
2	Precipitated Calcium Carbonate (Sturcal L)	258.7500	129.3750	64.6875	32.3438	21.635
3	Microcrystalline Cellulose (Vivapur 301)	439.7750	219.8875	109.9437	54.9719	36.770
4	Lactose Monohydrate (Pharmatose 200M)	270.0000	135.0000	67.5000	33.7500	22.575
5	Sodium Starch Glycolate Type A (Primojel®)	28.7500	14.3750	7.1875	3.5938	2.404
Binder Solution						
6	Hydroxy Propyl Cellulose (Klucel EF Pharm)	25.8750	12.9375	6.4688	3.2344	2.163
7	Polysorbate 80 (Kolliphor PS 80)	2.8750	1.4375	0.7188	0.3594	0.240
8	Purified Water@	QS	QS	QS	QS	N/A
Extra-granular						
9	Croscarmellose Sodium (Ac-Di-Sol® SD-711)	28.7500	14.3750	7.1875	3.5938	2.404
10	Magnesium Stearate (Veg.)	8.6250	4.3125	2.1563	1.0781	0.721
Total weight of core tablet (mg)		**1150.000**	**575.000**	**287.500**	**143.750**	N/A
Film Coating						
11	Opadry II Complete Film Coating System (White; 85F18422)	40.2500	20.1250	10.0625	5.0313	3.365
12	Hypromellose 2910, 6 mPa.s	2.8750	1.4375	0.7188	0.3594	0.240
13	Opadry® Complete Film Coating System ((Clear; YS-1R-7006)	2.8750	1.4375	0.7188	0.3594	0.240
14	Purified Water@	QS	QS	QS	QS	N/A
Total weight of coated tablet (mg)		**1196.000**	**598.000**	**299.000**	**149.499**	**100.000**

*Equivalent to 10 mg, 20 mg, 40 mg and 80 mg of Atorvastatin; @ Purified water evaporate during drying process and not a part of final product.

Table 65: Process Characterization/Optimization plan of Top Spray Granulation in Fluid Bed Processor (FBP)

Variables	**Ranges for Summary**		
	-1 (low)	**0 (medium)**	**1 (high)**
Inlet Air Temperature (°C)	50	60	70
Atomizing Air Pressure (AAP)	0.50	1.00	1.50
Peristaltic Pump (RPM)	20	30	40

Table 66: Experimental Design for Optimization of Top Spray Granulation at Fluid Bed Processor (FBP)

Design of Experiment		**Independent Variables (Intra-granular ingredient variation)**		
DOE Run No.	**Batch No.**	**Inlet Temp (°C)**	**Atomizing Air Pressure (bar)**	**Peristaltic Pump (RPM)**
1	20G047	50.00	1.50	40.00
2	20G048	70.00	1.50	40.00
3	20G049	50.00	0.50	40.00
4	20G050	50.00	1.50	20.00
5	20G051	50.00	0.50	20.00
6	20G052	70.00	1.50	20.00
7	20G053	60.00	1.00	30.00
8	20G054	60.00	1.00	30.00
9	20G055	70.00	0.50	20.00
10	20G056	70.00	0.50	40.00

Table 67: Physical Characterization of Different Batches of Top Spray Granulation Optimization at Fluid Bed Processor (FBP) (Common Granules)

Batch No.	Strength	Granules LOD at 105°C (NMT 3.5%)	Granules Bulk Density	Granules Tapped Density	Carr's Index (%)	Hausner Ratio	Flow Character
20G047	80 mg and 10 mg	1.50%	0.47	0.57	17.54	1.21	Fair
20G048		1.07%	0.48	0.55	12.73	1.15	Good
20G049		1.38%	0.55	0.66	16.67	1.20	Fair
20G050		1.29%	0.46	0.55	16.36	1.20	Fair
20G051		1.50%	0.45	0.52	13.46	1.16	Good
20G052		1.39%	0.45	0.56	19.64	1.24	Fair
20G053		1.75%	0.46	0.57	19.30	1.24	Fair
20G054		1.07%	0.49	0.59	16.95	1.20	Fair
20G055		1.24%	0.44	0.53	16.98	1.20	Fair
20G056		1.19%	0.54	0.67	19.40	1.24	Fair
Ref. LNB		**R&D/0221**					

Table 68: Physical Characterization of Different Batches of Top Spray Granulation Optimization at Fluid Bed Processor (FBP) (Core Tablet)

Batch No.	Strength	Uniformity of Weight (mg) Target: 1150.000 mg ± 5.0% (1092.500-1207.500) mg			Hardness (Kp)			Friability (%) (Target: NMT 1.0% w/w on NLT 6.50 g Tablets)
		Min.	Max.	Avg.	Min.	Max.	Avg.	
20G047A	80 mg	1141.87	1163.34	1158.99	-	-	-	0.02%
20G048A		1140.93	1166.51	1152.88	15.72	19.76	18.59	-
20G049A		1142.39	1154.93	1149.70	-	-	-	-
20G050A		1147.57	1168.43	1157.00	18.18	20.98	19.54	0.07%
20G051A		1144.15	1166.65	1154.81	18.00	19.34	18.74	0.02%
20G052A		1152.93	1161.45	1156.94	19.28	22.48	20.64	0.02%
20G053A		1152.01	1165.91	1158.39	-	-	-	-
20G054A		1141.76	1166.31	1158.24	16.77	20.54	18.64	0.05%
20G055A		1140.61	1165.31	1153.48	15.01	18.08	16.59	0.10%
20G056A		1144.21	1166.38	1158.77	15.19	18.91	18.02	0.02%
Ref. LNB		**R&D/0221, R&D/0226**						

Table 69: Physical Characterization of Different Batches of Top Spray Granulation Optimization at Fluid Bed Processor (FBP) (Core Tablet)

Batch No.	**Strength**	**Uniformity of Weight (mg) Target: 143.750 mg ± 5.0% (136.563-150.938) mg**			**Hardness (Kp)**			**Friability (%) (Target: NMT 1.0% w/w on NLT 6.50 g Tablets)**
		Min.	**Max.**	**Avg.**	**Min.**	**Max.**	**Avg.**	
20G047B	10 mg	141.43	146.83	145.54	8.07	9.04	8.53	0.04%
20G048B		141.24	146.29	143.43	7.25	9.25	8.38	0.05%
20G049B		142.56	147.77	144.66	7.45	8.65	7.98	0.15%
20G050B		140.13	145.58	142.61	7.2	9.25	8.59	0.03%
20G051B		141.45	145.47	143.22	7.82	9.03	8.60	0.04%
20G052B		138.72	144.94	143.00	7.88	10.79	8.92	0.08%
20G053B		141.90	148.15	144.18	6.8	8.29	7.52	0.12%
20G054B		142.29	146.77	144.24	7.50	8.57	7.94	0.05%
20G055B		142.94	145.85	144.68	7.71	8.65	8.16	0.06%
20G056B		144.26	149.28	146.17	7.30	8.65	7.92	0.07%
Ref. LNB		**R&D/0221, R&D/0226**						

Table 70: Dissolution Data of Different Batches of Generic Atorvastatin Calcium Tablets USP, 80 mg and 10 mg under Top Spray Granulation Optimization at Fluid Bed Processor (Core tablet)

Dissolution Media	pH 6.8 Phosphate Buffer								
Apparatus	Paddle (USP Apparatus II)								
Volume	900 mL								
Speed	75 RPM								
% Drug Release in 30 min									
80 mg					**10 mg**				
Batch No.	**Avg.**	**Min.**	**Max.**	**% RSD**	**Batch No.**	**Avg.**	**Min.**	**Max.**	**% RSD**
20G047A	87	86	88	0.9	20G047B	86	84	87	1.2
20G048A	88	87	90	0.9	20G048B	86	85	87	1.1
20G049A	90	89	92	1.3	20G049B	88	87	89	0.8
20G050A	92	90	94	1.6	20G050B	88	85	90	2.0
20G051A	90	88	91	1.4	20G051B	90	90	90	0.3
20G052A	91	89	92	1.3	20G052B	87	86	88	1.0
20G053A	87	86	88	1.2	20G053B	86	85	86	0.6
20G054A	87	87	88	0.7	20G054B	85	84	88	1.8
20G055A	91	90	93	0.8	20G055B	89	88	90	1.3
20G056A	88	86	90	1.4	20G056B	85	83	87	1.4
Ref. LNB	**R&D/0213, R&D/0215**								

Table 71: Assay Result for Different Batches of Generic Atorvastatin Calcium Tablets USP, 80 mg and 10 mg Tested under Top Spray Granulation Optimization at Fluid Bed Processor (Core tablet)

80 mg		**10 mg**	
Batch No.	**% Assay (Limit: NLT 94.5% and NMT 105.0% of the labeled amount of Atorvastatin)**	**Batch No.**	**% Assay (Limit: NLT 94.5% and NMT 105.0% of the labeled amount of Atorvastatin)**
20G047A	100.2	20G047B	101.0
20G048A	100.2	20G048B	100.7
20G049A	97.0	20G049B	99.0
20G050A	99.6	20G050B	100.7
20G051A	99.4	20G051B	102.5
20G052A	98.6	20G052B	97.2
20G053A	99.9	20G053B	96.9
20G054A	100.3	20G054B	97.8
20G055A	99.5	20G055B	100.2
20G056A	100.8	20G056B	99.8
Ref. LNB	**R&D/0203, R&D/0211, R&D/0212**		

Table 72: Impurity Result for Different Batches of Generic Atorvastatin Calcium Tablets USP, 80 mg Tested under Top Spray Granulation Optimization at Fluid Bed Processor (Core tablet)

Impurity Name	**20G047 A**	**20G048 A**	**20G049 A**	**20G050 A**	**20G051 A**	**20G052 A**	**20G053 A**	**20G054 A**	**20G055 A**	**20G056 A**
Atorvastatin pyrrolidone analog (NMT 0.5 %)	0.05	0.05	0.06	0.05	0.06	0.05	0.05	0.05	0.05	0.05
Atorvastatin related compound H (NMT 1.0 %)	0.04	0.04	0.04	0.04	0.04	0.05	0.04	0.04	0.05	0.04
Atorvastatin epoxypyrrolooxazin 6-hydroxy analog (NMT 0.5 %)	ND	ND	ND	ND	ND	ND	0.02	0.02	ND	ND
Atorvastatin epoxypyrrolooxazin 7-hydroxy analog (NMT 0.5 %)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Atorvastatin epoxy THF analog &	0.02	0.03	0.02	0.02	0.02	0.02	0.03	0.02	0.02	0.02

Impurity Name	**20G047 A**	**20G048 A**	**20G049 A**	**20G050 A**	**20G051 A**	**20G052 A**	**20G053 A**	**20G054 A**	**20G055 A**	**20G056 A**
Atorvastatin related Compound D (NMT 1.5 %)										
Any other unspecified degradation product (NMT 0.2 %)	0.04	0.04	0.04	0.04	0.05	0.04	0.04	0.04	0.04	0.04
Total impurities (NMT 4.0 %)	0.20	0.21	0.21	0.18	0.22	0.21	0.21	0.21	0.20	0.18
Ref. LNB	**R&D/0211, R&D/0212**									

Table 73: Impurity Result for Different Batches of Generic Atorvastatin Calcium Tablets USP, 10 mg Tested under Top Spray Granulation Optimization at Fluid Bed Processor (Core tablet)

Impurity Name	**20G047 B**	**20G048 B**	**20G049 B**	**20G050 B**	**20G051 B**	**20G052 B**	**20G053 B**	**20G054 B**	**20G055 B**	**20G056 B**
Atorvastatin pyrrolidone analog (NMT 0.5 %)	0.06	0.06	0.06	0.05	0.07	0.05	0.05	0.05	0.05	0.04
Atorvastatin related compound H (NMT 1.0 %)	0.05	0.04	0.04	0.04	0.05	0.05	0.05	0.04	0.05	0.05
Atorvastatin epoxypyrrolooxazin 6-hydroxy analog (NMT 0.5 %)	ND	ND	ND	ND	ND	ND	0.02	ND	0.03	ND
Atorvastatin epoxypyrrolooxazin 7-hydroxy analog (NMT 0.5 %)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Atorvastatin epoxy THF analog & Atorvastatin related compound D (NMT 1.5 %)	0.03	0.04	0.03	0.04	0.03	0.03	0.03	0.03	0.03	0.03
Any other unspecified degradation product (NMT 0.2 %)	0.04	0.04	0.04	0.04	0.04	0.03	0.04	0.04	0.04	0.04
Total impurities (NMT 4.0 %)	0.21	0.22	0.22	0.22	0.21	0.20	0.21	0.21	0.22	0.20
Ref. LNB	**R&D/0211, R&D/0212**									

Inference (Optimization of Top Spray Granulation at Fluid Bed Processor):

- LOD (at 105ºC auto mode) of all the ten (10) batches were found (1.07 – 1.75) %. Physical parameter tested for all these batches were found within acceptable limit i.e., uniformity of weight, appropriate hardness and friability lower than 0.2%.
- All impurities were found within the acceptance level. That means inlet air temperature range studied (50-70) ºC were suitable for drying operations of the Atorvastatin Calcium Tablets. As inlet air temperature is equipment independent parameter, hence, it will be maintained at same range throughout the scale up. On the other hand, air flow volume which is equipment dependent parameter need to be scale up to achieve the target output material attributes i.e. LOD of the granules, PSD and bulk density of the blend samples.
- Dissolution (average) of the core tablets at OGD method showed that more than 85% of the drug was released for all the batches of 80 mg and 10 mg within 30 minutes.
- Assay content of the core tablets of all the batches were within (97.0- 100.8) % for 80 mg and (97.2- 102.5) % for 10 mg.

Table 74 describes the risk reduction for the fluid bed processor step as a result of the development studies and justification is given below Table 75.

Table 74: Updated Risk Assessment of the Top Spray Granulation and Size Reduction Stage Variables on Output Materials CQAs

Output material CQA	**Top Spray Granulation Process Variables**				**Size Reduction Stage Variables**	
	Inlet Temperature (ºC)	**Inlet Air Volume (CFM)**	**Peristaltic Pump (RPM)**	**Atomizing Air Pressure (Bar)**	**Size reduction equipment**	**Mesh size/Screen Size**
Granules size distribution	Low*	Medium	Medium	Low*	Low*	Low*
Granules bulk density	Low	Medium	Medium	Low*	Low*	Low*
Granules LOD	Low*	Medium*	Low*	Low	Low	Low
Dissolution	Low	Low	Low	Low	Low	Low
Degradation Products	Low*	Low	Low	Low	Low	Low

***The level of risk is reduced from the initial risk assessment.**

Table 75: Justification for the Reduced Risk of Top Spray Granulation and Size Reduction Stage Variables on Output Materials CQAs

Input Material Attributes	Drug Products CQAs	Risk Category	Justification
Inlet Temperature (º C)	Granules size distribution	Low	Granules size distribution is less impacted at optimized inlet air temperature (50-70) ˚C. The risk is reduced to **Low.**
	Granules LOD	Low	Inlet temperature is optimized during product development and range is controlled in BMR to achieve LOD within range. The risk is reduced to **Low.**
	Degradation Products	Low	Inlet temperature is optimized during development and has no impact on the degradation product at the range studied. Therefore, the risk is reduced to **Low.**
Inlet Air Volume (CFM)	Granules size distribution	Medium	Inlet air volume is equipment dependent process parameters and need to be verified in commercial process validation. The risk is not lower from the initial risk assessment.
	Granules bulk density	Medium	
	Granules LOD	Medium	
Peristaltic Pump Speed (RPM)	Granules size distribution	Medium	Granules size distribution and bulk density is lees impacted by peristaltic pump speed. However, peristaltic pump speed need to verified at commercial scale following proposed batch record. Hence, risk is not reduced for granule size distribution and risk is reduced from high to medium for granule bulk density.
	Granules bulk density	Medium	
	Granules LOD	Low	Granules LOD is less impacted by peristaltic pump speed as inlet air temperature (50-70) ˚C is optimized during development. The risk is reduced to **Low.**
Atomizing Air Pressure (Bar)	Granules size distribution	Low	Atomizing Air Pressure is optimized during development and has no impact on the granules size distribution and bulk density at the range studied. Therefore, the risk is **Low.**
	Granules bulk density	Low	
Size reduction equipment	Granules size distribution	Low	Size reduction equipment and procedure (sifting-milling process) optimized during development and same will be used during commercial operation. The risk reduced to **Low**.
	Granules bulk density	Low	
Mesh size/Screen Size	Granules size distribution	Low	Mesh size/screen size for size reduction operation optimized during development and same will be used during commercial operation. The risk reduced to **Low**.
	Granules bulk density	Low	

2.2.3.3 Blending and Lubrication Process Optimization

The initial risk assessment of the overall manufacturing process presented in Table 60 and Table 61 identified the risk of the final blending and lubrication step to impact tablet dissolution as high. Number of revolutions identified as most potentially critical process parameters for further evaluation to establish limits for these CPPs (and CMAs) within which the quality of drug product will be assured. The blending and lubrication process variables that could potentially impact tablet dissolution were identified and their associated risk was evaluated. Table 76 presents the initial risk assessment of the final blending and lubrication step and Justification is given below Table 77.

Table 76: Initial Risk Assessment of the Extra-granular Blending and Lubrication Process Variables

Drug Products CQAs	**Extra-granular Blending and Lubrication Process Variables**						
	Granules PSD	**Glidant and Lubricant**	**Blender Fill Level**	**Number of Revolutions**	**Order of Addition**	**Discharge Method**	**Holding Time**
Blend Uniformity (BU)	Medium	Low	Low	High	Low	Low	Low
Blend Assay	Medium	Low	Low	High	Low	Low	Low

Table 77: Justification for the Initial Risk Assessment of the Extra-granular Blending and Lubrication Process

Variables	**Drug Products CQAs**	**Risk Category**	**Justification**
Granule PSD	Blend uniformity	Medium	Granule PSD has impact on BU and assay. However, granules PSD controlled at earlier steps. The risk is **Medium.**
	Blend assay	Medium	
Glidant and Lubricant	Blend uniformity	Low	Lubricating agent and glidant used in small amount. So lubricating agent is unlikely impact the BU/assay. The risk is **Low.**
	Blend assay	Low	
Blender fill level	Blend uniformity	Low	The mixer fill level depends on equipment capacity, blend bulk density and batch size. Blender fill level may affect mixing dynamics. However, occupancy used during blending is within equipment manufacturer recommended range. The risk is **Low**.
	Blend assay	Low	

Variables	**Drug Products CQAs**	**Risk Category**	**Justification**
Number of revolutions	Blend uniformity	High	Number of revolutions has directly impact on BU and assay. However, due to low API content (around 7.3%) in the formulation the risk is **High.**
	Blend assay	High	
Order of addition	Blend uniformity	Low	Order of addition are unlikely to impact the BU, flow ability and assay. The risk is **Low**.
	Blend assay	Low	
Discharge method	Blend uniformity	Low	Discharge method has no impact on BU and assay in product with high API content. The risk is **Low.**
	Blend assay	Low	
Holding time	Blend uniformity	Low	Holding time has no impact on BU and assay in product with high API content. The risk is **Low.**
	Blend assay	Low	

Based on current understanding No. of revolution are considered as potential critical process parameter. Bin blender was selected for blending stage optimization summary based on availability of blender.

Table 78: Manufacturing Formula for Process Optimization summary (Blending and Lubrication)

S/N	Ingredients	Amount (mg/ Tablet)				(% w/w to the core tablet)
		80 mg	40 mg	20 mg	10 mg	
Intra-granular						
1	Atorvastatin Calcium Trihydrate USP*	86.6000	43.3000	21.6500	10.8250	7.241
2	Precipitated Calcium Carbonate (Sturcal L)	258.7500	129.3750	64.6875	32.3438	21.635
3	Microcrystalline Cellulose (Vivapur 301)	439.7750	219.8875	109.9437	54.9719	36.770
4	Lactose Monohydrate (Pharmatose 200M)	270.0000	135.0000	67.5000	33.750	22.575
5	Sodium Starch Glycolate Type A (Primojel®)	28.7500	14.3750	7.1875	3.5938	2.404
Binder Solution						
6	Hydroxy Propyl Cellulose (Klucel EF Pharm)	25.8750	12.9375	6.4688	3.2344	2.163
7	Polysorbate 80 (Kolliphor PS 80)	2.8750	1.4375	0.7188	0.3594	0.240
8	Purified Water@	QS	QS	QS	QS	N/A
Extra-granular						
9	Croscarmellose Sodium (Ac-Di-Sol® SD-711)	28.7500	14.3750	7.1875	3.5938	2.404
10	Magnesium Stearate (Veg.)	8.6250	4.3125	2.1563	1.0781	0.721
Total weight of core tablet (mg)		**1150.000**	**575.000**	**287.500**	**143.750**	N/A
Film Coating						
11	Opadry II Complete Film Coating System (White; 85F18422)	40.2500	20.1250	10.0625	5.0313	3.365
12	Hypromellose 2910, 6 mPa.s	2.8750	1.4375	0.7188	0.3594	0.240
13	Opadry® Complete Film Coating System ((Clear; YS-1R-7006)	2.8750	1.4375	0.7188	0.3594	0.240
14	Purified Water@	QS	QS	QS	QS	N/A
Total weight of coated tablet (mg)		**1196.000**	**598.000**	**299.000**	**149.499**	**100.000**

*Equivalent to 10 mg, 20 mg, 40 mg and 80 mg of Atorvastatin; @ Purified water evaporate during drying process and not a part of final product.

Table 79: Process Characterization/Optimization Plan for Blending and Lubrication

Pre-Lubrication Optimization			**Lubrication Optimization**		
Variables	**Range for Optimization**		**Variables**	**Range for Optimization**	
	-1 (Low)	**1 (High)**		**-1 (Low)**	**1 (High)**
Blending Time (minutes)	6	10	Lubrication Time (minutes)	3	5
Number of Revolution	60	100	Number of Revolution	30	50
Sample Point	1st sample	2nd sample	Sample Point	1st sample	2nd sample

Table 80: Response/Dependent Variables of Blending and Lubrication Optimization Stage

Batch No.	200044 (Common blend)			
Blender Size	40 L			
Blender Speed	10 RPM			
Stage	Pre-Lubrication Time		Lubrication Time	
Blending time	6 minutes	10 minutes	3 minutes	5 minutes
Number of Revolution	60	100	30	50
Sampling Location	**Blend Uniformity (% of Label Claim)**		**Blend Uniformity (% of Label Claim)**	
1	94.1	94.8	97.9	97.0
2	100.7	98.8	103.7	99.6
3	98.9	98.2	101.5	102.4
4	98.3	104.5	100.4	98.8
5	99.6	100.9	99.9	101.1
6	96.3	96.2	98.2	98.7
7	98.3	99.0	98.0	99.5
Avg.	98.0	98.9	99.9	99.6
% RSD	2.2	3.2	2.1	1.8
Min.	94.1	94.8	97.9	97.0
Max.	100.7	104.5	103.7	102.4
	% Assay Content		% Assay Content	
	105.0	103.8	103.0	103.0
Ref. LNB	**R&D/0203, R&D/0211**			

Table 81 describes the risk reduction for the blending and lubrication step as a result of the development studies and justification given in below Table 82.

Table 81: Updated Risk Assessment of the Extra-granular Blending and Lubrication Process Variables

Output material CQAs	**Blending Process Variables**						
	Granules PSD	**Glidant and Lubricant**	**Blender Fill Level**	**Number of Revolutions**	**Order of Addition**	**Discharge Method**	**Holding Time**
Blend Uniformity	Low*	Low	Low	Low*	Low	Low	Low
Blend assay	Low*	Low	Low	Low*	Low	Low	Low

***The level of risk is reduced to Low from the initial risk assessment.**

Table 82: Justification for the Reduced Risk of the Extra-granular Blending and Lubrication Process

Variables	**Drug Products CQAs**	**Risk Category**	**Justification**
Granule PSD	Blend uniformity	Low	Granules PSD obtained using adopted top spray granulation and drying process for Atorvastatin Calcium Tablets USP are suitable to meet the consistent blend uniformity and blend assay. The risk is reduced to **Low.**
	Blend Assay	Low	
Number of revolutions	Blend uniformity	Low	Number of revolutions is optimized and controlled in BMR. The risk reduced to **Low.**
	Blend Assay	Low	

Inference (Blending and Lubrication):

Within studied range of number of revolutions, blend uniformity in both pre-lubrication (blending) and lubrication stages met predefined acceptance criteria. Based on summary outcomes, 60-100 revolution in pre-lubrication (blending) and 30-50 revolution in lubrication stage will be considered as design space for commercial scale up and post approval changes.

2.2.3.4 Compression Process Optimization

Initial risk assessment of the compression process variables based on the initial risk assessment of the overall manufacturing process. Process variables that could potentially impact physical attributes are identified and their associated risks were evaluated. Turret speed and feeder speed are identified as most potentially critical process parameters for further evaluation to establish limits for these CPPs (and CMAs) within which the quality of drug product will be assured. Initial risk assessment of the compression process variables is summarized in Table 83 and justification is given below Table 84.

Table 83: Initial Risk Assessment of the Compression Process Variables

Output material CQA	**Compression Process Variables**					
	Input Material Attributes		**Compression Machine Variables**			
	Blend Uniformity	**Blend Assay**	**Feeder Type and Speed**	**Pre-compression force/thickness**	**Main compression force/thickness**	**Press Speed (RPM)**
Assay	High	High	High	Low	Low	High
Content uniformity	High	High	High	Low	Low	High
Dissolution	Low	Low	Medium	Medium	Medium	Medium
Tablet Appearance	Low	Low	Low	Low	Medium	Medium
Hardness	Low	Low	Medium	Medium	High	Medium

Table 84: Justification of Initial Risk Assessment of the Compression Process Variables

Variables	**Drug Product CQAs**	**Risk Category**	**Justification**
Blend Uniformity (BU)	Assay	High	Content uniformity and tablet assay largely depends on the uniformity of blend. The low concentration of API (around 7.3% w/w) and poor flow ability may impact on assay and content uniformity. Granules uniformity which affects assay and content uniformity is controlled by earlier steps. Therefore, the risk is **High.**
	Content uniformity	High	
	Dissolution	Low	Blend uniformity has no impact on tablet dissolution, tablet appearance and tablet hardness. The risk is **Low.**
	Tablet Appearance	Low	

Variables	Drug Product CQAs	Risk Category	Justification
	Hardness	Low	
Blend assay	Assay	High	Blend assay has direct impact on tablet assay and Content uniformity. The low concentration of API (around 7.3% w/w) and poor flow ability may impact on assay and content uniformity. The risk is **High.**
	Content uniformity	High	
	Dissolution	Low	Blend assay is unlikely to impact dissolution, tablet appearance and hardness. The risk is **Low.**
	Tablet Appearance	Low	
	Hardness	Low	
Feeder Type and Speed	Assay	High	Feeder type (Gravity vs. Force Feeder) and feeder speed is likely to impact tablet weight variation during compression stage which can impact the uniformity of the dosage unit for low API containing drug product. Moreover, granules produce by top spray granulation is porous and friable in nature where there is a chance for weight variation during compression stage following breakdown of the granules due to uncontrolled feeder speed. The risk is **High.**
	Content uniformity	High	
	Dissolution	Medium	Feeder type and speed can impact tablet dissolution (i.e. due to over lubrication with impeller speed of feeder). The risk is **Medium** considering the BCS class II molecule**.**
	Tablet Appearance	Low	Feeder type and speed has no impact on tablet appearance. The risk is **Low.**
	Hardness	Medium	Increase in force feeder speed can reduce tablet tensile strength and tablet ability. The risk is **Medium.**
Pre-compression force/thickness	Assay	Low	Pre-compression force is unlikely to impact Tablet assay. The risk is **Low.**
	Content uniformity	Low	Content uniformity is dominated by BU and flowability and is unrelated to pre-compression force. The risk is **Low.**
	Dissolution	Medium	A greater than optimal pre-compression force may cause lamination. A lower than optimal pre- compression force may trap air in the tablets, leading to capping. Either scenario could impact disintegration and dissolution. Adjustment may be needed. The risk is **Medium**.
	Tablet Appearance	Low	Pre-compression force has no impact on Tablet appearance. The risk is **Low.**
	Hardness	Medium	Pre-compression force mainly required for removing the entrapped air during compression. The hardness of the compressed tablet prominently governed by main compression force. The risk is **Medium.**

Variables	Drug Product CQAs	Risk Category	Justification
Main compression force/thickness	Assay	Low	Main compression force has no impact on tablet assay. The risk is **Low.**
	Content uniformity	Low	Content uniformity is dominated by BU and flowability and is unrelated to main compression force. The risk is **Low.**
	Dissolution	Medium	Compression force may affect tablet hardness and friability and, ultimately on dissolution. The risk is **Medium.**
	Tablet Appearance	Medium	At high compression force material with low melting point forms an inclusion complex due to heat generated during compression which can reduce dissolution to large extent. Even physical appearance of tablets can indicate its nature change. The risk is **Medium.**
	Hardness	High	A little change in compression force can significantly affect the tablet hardness and disintegration time. Tablets producing with very low and high compression forces can be very soft or hard for the intended purposed. The compression force should, therefore, carefully be controlled to produce tablets within specifications. Both tablet hardness and disintegration time remains lower at lower applied compression forces and increases with increasing applied forces. Therefore, the risk is **High.**
Press Speed (RPM)	Assay	High	A faster than optimal press speed may cause inconsistent die filling and weight variability which may then impact Assay and Content uniformity. For efficiency, the press speed will be set as fast as practically possible without adversely impacting tablet quality. The risk is **High.**
	Content uniformity	High	
	Dissolution	Medium	Press can impact tablet dissolution via tablet hardness. However, tablet hardness mainly controlled by compression force. The risk is **Medium**.
	Tablet Appearance	Medium	The effects of speed of compression has fundamental importance in the compaction of powdered materials ultimately on tablet appearance and hardness. However, tablet hardness mainly controlled by compression force. The risk is considered **Medium**.
	Hardness	Medium	

Based on current understanding turret speed and feeder speed are considered as potential critical process parameter which will may impact on drug product CQAs (i.e. dissolution). To evaluate impact of feeding system (Gravity feeder vs. Force feeder) on drug product CQAs or intermediate, one DOE run with gravity feeder was also considered. Three tier approach was taken to characterization and/ or optimization of compression process variables.

- Optimization of compression machine variables
- Optimization summary for hardness range establishment

Table 85: Manufacturing Formula for Process Optimization summary (Compression Optimization)

S/N	Ingredients	Amount (mg/ Tablet)				(% w/w to the core tablet)
		80 mg	40 mg	20 mg	10 mg	
Intra-granular						
1	Atorvastatin Calcium Trihydrate USP*	86.6000	43.3000	21.6500	10.8250	7.241
2	Precipitated Calcium Carbonate (Sturcal L)	258.7500	129.3750	64.6875	32.3438	21.635
3	Microcrystalline Cellulose (Vivapur 301)	439.7750	219.8875	109.9437	54.9719	36.770
4	Lactose Monohydrate (Pharmatose 200M)	270.0000	135.0000	67.5000	33.750	22.575
5	Sodium Starch Glycolate Type A (Primojel®)	28.7500	14.3750	7.1875	3.5938	2.404
Binder Solution						
6	Hydroxy Propyl Cellulose (Klucel EF Pharm)	25.8750	12.9375	6.4688	3.2344	2.163
7	Polysorbate 80 (Kolliphor PS 80)	2.8750	1.4375	0.7188	0.3594	0.240
8	Purified Water@	QS	QS	QS	QS	N/A
Extra-granular						
9	Croscarmellose Sodium (Ac-Di-Sol® SD-711)	28.7500	14.3750	7.1875	3.5938	2.404
10	Magnesium Stearate (Veg.)	8.6250	4.3125	2.1563	1.0781	0.721
Total weight of core tablet (mg)		**1150.000**	**575.000**	**287.500**	**143.750**	N/A
Film Coating						
11	Opadry II Complete Film Coating System (White; 85F18422)	40.2500	20.1250	10.0625	5.0313	3.365

S/N	Ingredients	Amount (mg/ Tablet)				(% w/w to the core tablet)
		80 mg	40 mg	20 mg	10 mg	
12	Hypromellose 2910, 6 mPa.s	2.8750	1.4375	0.7188	0.3594	0.240
13	Opadry® Complete Film Coating System ((Clear; YS-1R-7006)	2.8750	1.4375	0.7188	0.3594	0.240
14	Purified Water@	QS	QS	QS	QS	N/A
Total weight of coated tablet (mg)		**1196.000**	**598.000**	**299.000**	**149.499**	**100.000**

*Equivalent to 10 mg, 20 mg, 40 mg and 80 mg of Atorvastatin;
@ Purified water evaporate during drying process and not a part of final product

Table 86: Process Characterization/Optimization Plan of Compression Variables

Compression Variables	Range for Optimization		
	-1 (Low)	0 (medium)	1 (high)
Turret Speed (RPM)	15	20	25
Feeder Speed (%)	100	150	200

Table 87: Design of Experiment run for Optimization of Compression Variables

Design of Experiment		Independent Variables (Intra-granular ingredient variation)	
DOE Run No.	Batch No.	Turret Speed (RPM)	Feeder Speed (%)
1	20G044A	25	200
2	20G044B	20	150
3	20G044C	15	200
4	20G044D	25	100
5	20G044E	15	100
6	20G044F	20	150
7	20G044G	Gravity Feeder	

Table 88: Physical Characterization of Different Batches at Compression Optimization Stage (Core tablet)

Batch No.	**Strength**	**Uniformity of Weight (mg) Target: 1150.000 mg ± 5.0% (1092.500-1207.500) mg**			**Hardness (Kp)**			**Disintegration Time Target: NMT 15.0 minutes determined on 6 tablets (without disc)**		**Friability (%) (Target: NMT 1.0% w/w on NLT 6.50 g Tablets)**
		Min.	**Max.**	**Avg.**	**Min.**	**Max.**	**Avg.**	**FT**	**LT**	
20G044A1	80 mg	1145.11	1165.40	1158.94	14.43	20.17	17.90	1'25"	1'33"	0.00%
20G044B1		1140.97	1164.24	1151.99	18.01	20.51	19.32	1'37"	1'41"	0.03%
20G044C1		1149.21	1162.84	1155.74	18.05	20.70	19.66	1'39"	1'47"	0.02%
20G044D1		1143.08	1158.82	1150.71	19.22	20.35	19.82	1'23"	1'34"	0.03%
20G044E1		1144.14	1163.42	1152.86	18.65	20.36	19.47	1'50"	2'2"	0.05%
20G044F1		1142.81	1163.00	1154.20	18.90	20.47	19.44	1'37"	1'42"	0.12%
20G044G1		1140.23	1163.56	1151.96	19.04	22.19	20.31	1'22"	1'27"	0.06%
Ref. LNB		**R&D/0221, R&D/0226**								

Table 89: Physical Characterization of Different Batches at Compression Optimization Stage (Core tablet)

Batch No.	**Strength**	**Uniformity of Weight (mg) Target: 143.750 mg ± 5.0% (136.563-150.938) mg**			**Hardness (Kp)**			**Disintegration Time Target: NMT 15.0 minutes determined on 6 tablets (without disc)**		**Friability (%) (Target: NMT 1.0% w/w on NLT 6.50 g Tablets)**
		Min.	**Max.**	**Avg.**	**Min.**	**Max.**	**Avg.**	**FT**	**LT**	
20G044A2	10 mg	143.07	148.42	146.00	7.33	9.42	8.36	49"	57"	0.04%
20G044B2		143.38	147.17	145.36	7.82	8.97	8.54	52"	55"	0.06%
20G044C2		142.95	146.08	144.61	7.36	8.90	7.96	44"	48"	0.02%
20G044D2		143.33	145.92	144.87	7.78	8.71	8.23	47"	51"	0.14%
20G044E2		142.74	145.98	144.24	6.81	8.53	7.93	42"	51"	0.00%
20G044F2		142.23	146.20	144.62	6.66	7.33	7.13	43"	47"	0.05%
20G044G2		142.84	146.40	144.70	6.72	7.47	7.01	45"	50"	0.10%
Ref. LNB		**R&D/0221, R&D/0226**								

Table 90: Dissolution Data for Different Batches of Generic Atorvastatin Calcium Tablets USP, 80 mg and 10 mg Tested under Compression Optimization Stage (Core tablet)

Dissolution Media	pH 6.8 Phosphate Buffer								
Apparatus	Paddle (USP Apparatus II)								
Volume	900 mL								
Speed	75 RPM								
% Drug Release in 30 min									
80 mg					**10 mg**				
Batch No.	**Avg.**	**Min.**	**Max.**	**% RSD**	**Batch No.**	**Avg.**	**Min.**	**Max.**	**% RSD**
20G044A1	89	89	90	0.5	20G044A2	90	88	93	2.0
20G044B1	92	91	93	0.7	20G044B2	91	88	92	1.3
20G044C1	93	92	94	1.0	20G044C2	92	90	93	1.3
20G044D1	92	91	93	0.7	20G044D2	92	90	93	1.6
20G044E1	92	91	94	1.0	20G044E2	90	89	92	1.3
20G044F1	93	92	93	0.8	20G044F2	92	90	92	0.8
20G044G1	94	93	95	0.9	20G044G2	91	90	95	2.2
Ref. LNB	**R&D/0211, R&D/0213, R&D/0215**								

Table 91: Assay Result of Different Batches of Atorvastatin Calcium Tablets USP, 80 mg Tested under Compression Optimization Stage (Core tablet)

Strength: 80 mg		**Strength: 10 mg**	
Batch No.	**% Assay (Limit: NLT 94.5% and NMT 105.0% of the labeled amount of Atorvastatin)**	**Batch No.**	**% Assay (Limit: NLT 94.5% and NMT 105.0% of the labeled amount of Atorvastatin)**
20G044A1	101.6	20G044A2	100.0
20G044B1	102.7	20G044B2	100.6
20G044C1	102.7	20G044C2	99.0
20G044D1	101.7	20G044D2	100.2
20G044E1	101.1	20G044E2	99.3
20G044F1	101.9	20G044F2	99.4
20G044G1	101.1	20G044G2	96.9
Ref. LNB	**R&D/0203, R&D/0211, R&D/0212**		

Table 92: Content Uniformity Result of Different Batches of Atorvastatin Calcium Tablets USP 80 mg Tested under Compression Optimization Stage (Core tablet)

% Atorvastatin content							
Batch No.	**20G044A1**	**20G044B1**	**20G044C1**	**20G044D1**	**20G044E1**	**20G044F1**	**20G044G1**
Sample 1	98.1	99.2	99.1	100.5	97.4	97.7	97.0
Sample 2	100.2	100.4	98.3	99.1	97.3	96.4	97.2
Sample 3	97.2	97.7	100.4	98.6	97.3	96.5	96.9
Sample 4	97.3	97.0	98.9	99.1	97.1	97.1	98.2
Sample 5	95.7	98.8	98.3	98.0	96.4	94.7	97.7
Sample 6	97.3	98.0	99.2	98.0	95.4	96.7	97.0
Sample 7	97.8	99.4	98.5	96.7	97.8	98.5	95.7
Sample 8	99.0	100.3	98.5	98.0	97.5	97.7	98.5
Sample 9	98.2	98.2	101.1	98.5	96.1	96.1	97.0
Sample 10	98.7	99.4	99.5	97.7	95.7	96.9	96.4
Average	98.0	98.8	99.2	98.4	96.8	96.8	97.2
Minimum	95.7	97.0	98.3	96.7	95.4	94.7	95.7
Maximum	100.2	100.4	101.1	100.5	97.8	98.5	98.5
% RSD	1.2	1.1	0.9	1.0	0.9	1.1	0.8
Acceptance value ≤ 15	3.5	2.7	2.2	2.5	3.7	4.1	3.3
Ref. LNB	**R&D/0203, R&D/0211, R&D/0212, R&D/0213**						

Table 93: Content Uniformity Result of Different Batches of Atorvastatin Calcium Tablets USP, 10 mg Tested under Compression Optimization Stage (Core tablet)

% Atorvastatin content							
Batch No.	**20G044A2**	**20G044B2**	**20G044C2**	**20G044D2**	**20G044E2**	**20G044F2**	**20G044G2**
Sample 1	99.0	98.3	99.1	97.8	96.0	96.6	96.4
Sample 2	97.7	99.6	100.8	98.2	98.9	97.3	96.8
Sample 3	98.3	98.8	98.5	96.6	96.7	97.2	95.8
Sample 4	99.7	98.2	98.8	97.4	96.8	100.3	95.6
Sample 5	101.4	98.5	97.5	96.9	99.0	96.2	96.0
Sample 6	96.0	99.6	99.4	98.9	98.2	97.2	96.1

Sample 7	99.6	96.9	99.1	98.9	95.9	97.7	95.5
Sample 8	100.7	98.4	98.3	96.6	98.2	98.3	95.3
Sample 9	97.1	99.0	97.9	98.4	97.2	98.9	97.6
Sample 10	98.9	98.0	97.8	97.5	97.3	97.1	94.7
Average	98.9	98.5	98.7	97.7	97.4	97.7	96.0
Minimum	96.0	96.9	97.5	96.6	95.9	96.2	94.7
Maximum	101.4	99.6	100.8	98.9	99.0	100.3	97.6
% RSD	1.6	0.8	1.0	0.9	1.2	1.2	0.9
Acceptance value ≤ 15	3.9	1.9	2.3	2.9	3.8	3.7	4.5
Ref. LNB	**R&D/0207, R&D/0211, R&D/0212, R&D/0213**						

Inference (Optimization of Compression Stage):

- Physical parameter evaluated for all the seven (07) batches manufactured by variation of turret speed, feeder speed and feeder type were found within acceptable limit i.e., disintegration within 5 minutes, uniformity of weight at acceptable range, appropriate hardness and low friability.

- Dissolution (average) of the core tablets at OGD method showed that more than 85% of the drug was released within 30 minutes for all of the batches studied under compression stage optimization. Dissolution was not impacted by variation of turret, feeder type and force feeder speed.

- Uniformity of dosage unit by content uniformity for all of the batches studied under compression stage optimization were found within acceptable limit (Acceptance value <5).

- Assay content of all the batches were within (101.1- 102.7) % for 80 mg and (96.9- 100.6) % for 10 mg.

Table 94 describes the risk reduction for the compression step as a result of the development studies and justification is given below Table 95.

Table 94: Updated Risk Assessment of the Compression Process Variables

Output material CQAs	**Compression Process Variables**					
	Input Material Attributes		**Compression Machine Variables**			
	Blend Uniformity	**Blend Assay**	**Feeder Type and Speed**	**Pre compression force/thickness**	**Main compression force/thickness**	**Press Speed**
Assay	Medium*	Medium*	Low*	Low	Low	Medium*
Content uniformity	Medium*	Medium*	Low*	Low	Low	Medium*
Dissolution	Low	Low	Low*	Low	Low*	Low*
Tablet Appearance	Low	Low	Low	Low	Low*	Low*
Hardness	Low	Low	Low*	Low*	Medium*	Low*

***The level of risk is reduced from the initial risk assessment.**

Table 95: Justification of Reduced Risk of the Compression Process Variables

Variables	**Drug Product CQAs**	**Risk Assessment**	**Justification and Initial Strategy**
Blend uniformity (BU)	Assay	Medium	Blend uniformity is optimized during development and scale-up throughout the optimization of granulation, drying and size reduction steps. However, this attribute needs to be further verified at commercial scale for intended equipment. The level of risk is reduced from **High** to **Medium** from the initial risk assessment.
	Content uniformity	Medium	
Blend assay	Assay	Medium	As API percentage is around 7.3% w/w as well as blending and lubrication stage parameters is fixed at blend optimization stage (i.e. No. of revolution) that's why blend uniformity has impact on tablet assay and content uniformity. However, this attribute needs to be further verified at commercial scale for intended equipment. Therefore, the level of risk is reduced from **High** to **Medium** from the initial risk assessment.
	Content uniformity	Medium	
Feeder Type and Speed	Assay	Low	Tablet Assay, Content uniformity, hardness and dissolution is not impacted by Feeder Type (Gravity vs. Force Feeder) and Speed. The risk is reduced to **Low.**
	Content uniformity	Low	
	Dissolution	Low	
	Hardness	Low	

Variables	Drug Product CQAs	Risk Assessment	Justification and Initial Strategy
Pre-compression force/thickness	Dissolution	Low	Tablet hardness increases with compression force. Within the compression force range studied, the resulting tablet hardness did not adversely affect dissolution and > 90% dissolution at 30 min was achieved. The risk is reduced to **Low.**
	Hardness	Low	Pre-compression force is optimized during development and tablet hardness mainly controlled by main compression force. The risk is reduced to **Low**.
Main compression force/thickness	Dissolution	Low	Tablet hardness increases with compression force. Within the compression force range studied, the resulting tablet hardness did not adversely affect dissolution and > 90% dissolution at 30 min was achieved. The risk is reduced to **Low.**
	Tablet Appearance	Low	During compression optimization summary, within standard hardness range no lamination or capping occurred. The risk is reduced to **Low.**
	Hardness	Medium	Tablet hardness was not varied so much with standard main compression force and meet hardness requirement for this product. The risk is reduced from **High** to **Medium.**
Press Speed	Assay	Medium	Press speed is optimized during development and scale-up which need to be further validated at commercial scale for intended equipment. The level of risk is reduced from **High** to **Medium** the initial risk assessment.
	Content uniformity	Medium	
	Dissolution	Low	Within the hardness range studied, the resulting tablet hardness did not adversely affect dissolution. The risk is reduced to **Low.**
	Hardness	Low	
	Tablet Appearance	Low	Tablet Appearance is not impacted by the tableting machine speed. The risk is reduced to **Low.**

2.2.3.5 Coating Process Optimization

Initial Risk Assessment of the Coating Process Variables based on the initial risk assessment of the overall manufacturing process. Process variables that could potentially impact physical attributes are identified and their associated risks were evaluated. Inlet air temp, Atomizing air pressure and Spray Rate are identified as most potentially critical process parameters for further evaluation to establish limits for these CPPs (and CMAs) within which the quality of drug product will be assured. The results of the initial risk assessment of the compression process variables are summarized in Table 96 and justification is presented below Table 97.

Table 96: Initial Risk Assessment of the Coating Process Variables

Output material CQA	**Coating Process Variables**							
	Input Material Attributes			**Coating Machine Variables**				
	Core Tablet Appearance	**Hardness**	**Solid content**	**Inlet Air Temp. (ºC)**	**Inter Air Volume (CFM)**	**Atomizing Air Pressure (AAP)**	**Spray Rate (RPM)**	**Pan Speed (RPM)**
Appearance	Medium	Medium	Medium	Medium	Medium	High	High	Medium
Weight gain	Low	Medium	Medium	High	Medium	High	Medium	Medium
Dissolution	Low	Low	Low	Low	Low	Medium	Medium	Low
Degradation Product	Low	Low	Low	Medium	Low	Low	Medium	Low

Table 97: Justification of Initial Risk Assessment of the Coating Process Variables

Variables	**Output Material CQAs**	**Risk Category**	**Justification**
Core Tablet appearance	Appearance	Medium	Final appearance of the tablet depends on the appearance of the core tablet. Core tablet appearance control at earlier step. The risk is **Medium.**
	Weight gain	Low	Core tablet appearance is unlikely to impact weight gain, dissolution and degradation product. The risk is **Low.**
	Dissolution	Low	
	Degradation Product	Low	
Hardness	Appearance	Medium	Tablet hardness is likely to impact final product appearance as tablet with suboptimal hardness may not withstand with the rigor of the coating pan and removal of material from the surface may results in rough surface. The risk is considered **Medium** as tablets meet the friability requirements.
	Weight gain	Medium	Suboptimal hardness may lead to surface erosion which impacts the weight gain. The risk is **Medium**.
	Dissolution	Low	Hardness range established at earlier step and dissolution profile found similar for different tablets prepared with different hardness. The risk is **Low.**
	Degradation Product	Low	Hardness is unlikely to impact Degradation Product. The risk is **Low.**

Variables	**Output Material CQAs**	**Risk Category**	**Justification**
Solid content	Appearance	Medium	Higher solid content in coating solution may result in surface roughness of the tablet will be evaluated during development. The risk is **Medium.**
	Weight gain	Medium	Solution with higher solid content reduces the risk of weight gain but need optimization of the process parameters. The risk is **Medium.**
	Dissolution	Low	Percent of solid in solution is unlikely to impact dissolution and degradation product. The risk is **Low.**
	Degradation Product	Low	
Inlet Air Temp (ºC)	Appearance	Medium	Inlet air temperature variability may cause over drying of tablet and spray resulting rough surface and lead to sticking of tablets. The risk is **Medium.**
	Weight gain	High	High temperature may cause spray drying which can impact weight gain. The risk is **High.**
	Dissolution	Low	Inlet air temperature unlikely to impact dissolution. The risk is **Low.**
	Degradation Product	Medium	High product bed temperature may impact degradation products. However, atorvastatin calcium trihydrate is stable at solid state degradation. Therefore, the risk is **Medium.**
Inlet Air Volume (CFM)	Appearance	Medium	Inlet Air Volume higher/lower than optimal is likely to impact appearance. The risk is **Medium**.
	Weight gain	Medium	Inlet Air Volume higher than optimal is responsible for spray drying. The risk is **Medium**.
	Dissolution	Low	Inlet Air Volume is unlikely to impact tablet dissolution and degradation product. The risk is **Low.**
	Degradation Product	Low	
Atomizing Air Pressure (AAP)	Appearance	High	Tablet surface roughness is dependent on atomization air pressure. High AAP may impact on appearance of the tablet (i.e. surface roughness) and generates more fine droplets, which triggers spray drying (i.e. impact on weight gain) and low AAP may cause defects like sticking and picking due to formation of large droplet size. The risk is **High.**
	Weight gain	High	
	Dissolution	Medium	Atomizing Air Pressure may impact the uniformity of the coating which may impact the disintegration of the coated tablets ultimately on dissolution. However, water soluble materials used at film coating stage. Hence, the risk is **Medium.**
	Degradation Product	Low	Atomizing Air Pressure is unlikely to impact tablet dissolution and degradation products. The risk is **Low.**

Variables	Output Material CQAs	Risk Category	Justification
Spray Rate (RPM)	Appearance	High	Variability of spray rate may cause inadequate drying, twinning and sticking, orange peel effect. Thus spray rate will have a significant impact on surface roughness and weight gain. The optimization of spray rate is needed hence considered as **High** risk for appearance and **Medium** risk for weight gain.
	Weight gain	Medium	
	Dissolution	Medium	Variability of spray rate may impact the uniformity of the coating which may impact the disintegration of the coated tablets ultimately on dissolution. However, water soluble materials used at film coating stage. Hence, the risk is **Medium.**
	Degradation Products	Medium	Uncontrolled spray rate may impact the weight gain and moisture absorption during film coating stage which may impact the degradation product generation. However, core tablet hardness optimized in such a way so that moisture pick up during coating stage can be minimized. Hence, the risk is **Medium.**
Pan Speed (RPM)	Appearance	Medium	Pan speed may cause defects like sticking due to improper rotation of the tablet in the coating pan. Pan speed also ensure uniform spraying of tablet throughout the coating process. Pan speed will be controlled by visual observation during coating process. The risk is **Medium.**
	Weight gain	Medium	
	Dissolution	Low	Pan speed is unlikely to impact tablet dissolution and degradation products. The risk is **Low.**
	Degradation Product	Low	

The objective is to screen out critical process parameter (CPPs) from potential critical process parameter (p-CPPs) and to establish design space for CPPs as well as evaluation of their impact on intermediate CQAs or finished product CQAs. Based on current understanding inlet air temperature, spray rate and atomizing air pressure are identified as potential critical process parameter (p-CPPs) for optimization summary.

Table 98: Manufacturing Formula for Process Optimization summary (Coating Optimization)

S/N	Ingredients	Amount (mg/ Tablet)				(% w/w to the core tablet)
		80 mg	**40 mg**	**20 mg**	**10 mg**	
Intra-granular						
1	Atorvastatin Calcium Trihydrate USP*	86.6000	43.3000	21.6500	10.8250	7.241
2	Precipitated Calcium Carbonate (Sturcal L)	258.7500	129.3750	64.6875	32.3438	21.635
3	Microcrystalline Cellulose (Vivapur 301)	439.7750	219.8875	109.9437	54.9719	36.770
4	Lactose Monohydrate (Pharmatose 200M)	270.0000	135.0000	67.5000	33.750	22.575
5	Sodium Starch Glycolate Type A (Primojel®)	28.7500	14.3750	7.1875	3.5938	2.404
Binder Solution						
6	Hydroxy Propyl Cellulose (Klucel EF Pharm)	25.8750	12.9375	6.4688	3.2344	2.163
7	Polysorbate 80 (Kolliphor PS 80)	2.8750	1.4375	0.7188	0.3594	0.240
8	Purified Water@	QS	QS	QS	QS	N/A
Extra-granular						
9	Croscarmellose Sodium (Ac-Di-Sol® SD-711)	28.7500	14.3750	7.1875	3.5938	2.404
10	Magnesium Stearate (Veg.)	8.6250	4.3125	2.1563	1.0781	0.721
Total weight of core tablet (mg)		**1150.000**	**575.000**	**287.500**	**143.750**	N/A
Film Coating						
11	Opadry II Complete Film Coating System (White; 85F18422)	40.2500	20.1250	10.0625	5.0313	3.365
12	Hypromellose 2910, 6 mPa.s	2.8750	1.4375	0.7188	0.3594	0.240
13	Opadry® Complete Film Coating System ((Clear; YS-1R-7006)	2.8750	1.4375	0.7188	0.3594	0.240
14	Purified Water@	QS	QS	QS	QS	N/A
Total weight of coated tablet (mg)		**1196.000**	**598.000**	**299.000**	**149.499**	**100.000**

*Equivalent to 10 mg, 20 mg, 40 mg and 80 mg of Atorvastatin; @ Purified water evaporate during drying process and not a part of final product.

Table 99: Process Characterization/Optimization Plan of Coating Process Variables

Input Variables (p-CPPs)	**Range for Optimization**		
	-1 (low)	**0 (medium)**	**+1 (high)**
Inlet Air Temp. (°C)	50.00	60.00	70.00
Atomizing Air Pressure (Bar)	1.00	1.50	2.00
Spray Rate (RPM)	10.00	15.00	20.00

Table 100: Experimental Design for Atorvastatin Calcium Tablets USP at Coating Optimization Summary

Design of Experiment					**Independent Variables (Intra-granular ingredient variation)**		
DOE Run No.	**Batch No.**	**Strength**	**Batch No.**	**Strength**	**Inlet Temp (°C)**	**Atomizing Air Pressure (bar)**	**Spray Rate (RPM)**
1	20H018A1	80 mg	20H018B1	10 mg	60.00	1.50	10.00
2	20H018A2		20H018B2		60.00	1.50	20.00
3	20H018A3		20H018B3		60.00	2.00	15.00
4	20H018A4		20H018B4		60.00	1.00	15.00
5	20H018A5		20H018B5		50.00	1.50	15.00
6	20H018A6		20H018B6		60.00	1.50	15.00
7	20H018A7		20H018B7		70.00	1.00	15.00

Table 101: Dissolution Data of Different Batches of Atorvastatin Calcium Tablets USP, 80 mg and 10 mg at Coating Optimization Summary (Coated tablet)

Dissolution Media	pH 6.8 Phosphate Buffer								
Apparatus	Paddle (USP Apparatus II)								
Volume	900 mL								
Speed	75 RPM								
% Drug Release in 30 min									
80 mg					**10 mg**				
Batch No.	**Avg.**	**Min.**	**Max.**	**% RSD**	**Batch No.**	**Avg.**	**Min.**	**Max.**	**% RSD**
20H018A1	90	89	92	1.5	20H018B1	89	88	91	1.2
20H018A2	93	90	96	2.9	20H018B2	90	89	92	1.1
20H018A3	93	92	96	1.6	20H018B3	91	90	93	1.6
20H018A4	96	95	97	0.7	20H018B4	90	88	91	1.3
20H018A5	94	92	95	1.1	20H018B5	89	87	92	1.9
20H018A6	93	93	95	1.2	20H018B6	91	90	92	0.8
20H018A7	97	95	98	1.1	20H018B7	89	88	91	1.2
Ref. LNB	**R&D/0209, R&D/0215**								

Table 102: Impurity Result of Different Batches of Atorvastatin Calcium Tablets USP, 80 mg at Coating Optimization Summary (Coated tablet)

Impurity Name	**Strength**	**20H018 A1**	**20H018 A2**	**20H018 A3**	**20H018 A4**	**20H018 A5**	**20H018 A6**	**20H018 A7**
Atorvastatin pyrrolidone analog (NMT 0.5 %)	80 mg	0.05	0.05	0.05	0.06	0.05	0.06	0.06
Atorvastatin related compound H (NMT 1.0 %)		0.05	0.04	0.05	0.05	0.05	0.04	0.05
Atorvastatin epoxypyrrolooxazin 6-hydroxy analog (NMT 0.5 %)		0.04	ND	ND	ND	0.03	ND	0.02
Atorvastatin epoxypyrrolooxazin 7-hydroxy analog (NMT 0.5 %)		ND	ND	ND	ND	ND	ND	ND
Atorvastatin epoxy THF analog & Atorvastatin related Compound D (NMT 1.5 %)		0.03	0.03	0.03	0.03	0.02	0.02	0.03
Any other unspecified degradation product (NMT 0.2 %)		0.04	0.04	0.04	0.04	0.04	0.04	0.04
Total impurities (NMT 4.0 %)		0.23	0.19	0.19	0.22	0.23	0.20	0.25
Ref. LNB		**R&D/0211, R&D/0212**						

Table 103: Impurity Result of Different Batches of Atorvastatin Calcium Tablets USP, 10 mg at Coating Optimization Summary (Coated tablet)

Impurity Name	**Strength**	**20H018 B1**	**20H018 B2**	**20H018 B3**	**20H018 B4**	**20H018 B5**	**20H018 B6**	**20H018 B7**
Atorvastatin pyrrolidone analog (NMT 0.5 %)	10 mg	0.05	0.05	0.05	0.06	0.05	0.05	0.05
Atorvastatin related compound H (NMT 1.0 %)		0.05	0.05	0.05	0.05	0.05	0.05	0.06
Atorvastatin epoxypyrrolooxazin 6-hydroxy analog (NMT 0.5 %)		0.03	ND	ND	ND	ND	ND	ND
Atorvastatin epoxypyrrolooxazin 7-hydroxy analog (NMT 0.5 %)		ND	ND	ND	ND	ND	ND	ND
Atorvastatin epoxy THF analog & Atorvastatin related Compound D (NMT 1.5 %)		0.03	0.03	0.03	0.03	0.01	0.03	0.03
Any other unspecified degradation product (NMT 0.2 %)		0.04	0.05	0.04	0.04	0.04	0.04	0.04
Total impurities (NMT 4.0 %)		0.26	0.23	0.20	0.24	0.19	0.23	0.24
Ref. LNB		**R&D/0211, R&D/0212**						

Inference (Optimization of Coating Stage):

- Dissolution (average) of the coated tablets at OGD method showed that more than 85% of the drug was released for all the batches within 30 minutes. Dissolution was not impacted by variation of inlet air temp, atomizing air pressure and spray rate.

- Impurities of the drug product were found at very low level for all the batches manufactured by variation of the coating process parameters.

Table 104 describes the risk reduction for the coating step as a result of the development studies and justification is given in Table 105.

Table 104: Updated Risk Assessment of the Coating Process Variables

Output material CQA	**Coating Process Variables**							
	Input Material Attributes			**Coating machine variables**				
	Core Tablet Appearance	**Hardness**	**Solid content**	**Inlet Air Temp. (º C)**	**Inter Air Volume (CFM)**	**Atomizing Air Pressure (AAP)**	**Spray Rate (RPM)**	**Pan Speed (RPM)**
Appearance	Low*	Low*	Low*	Low*	Medium	Low*	Medium*	Medium
Weight gain	Low	Low*	Low*	Low*	Medium	Low*	Low*	Medium
Dissolution	Low	Low	Low	Low	Low	Low*	Low*	Low
Degradation Product	Low	Low	Low	Low*	Low	Low	Low*	Low

***The level of risk is reduced from the initial risk assessment**

Table 105: Justification of Reduced Risk of the Coating Process Variables

Variables	**Output Material Attributes**	**Risk Category**	**Justification**
Core Tablet Appearance	Appearance	Low	Tablet appearance is not impacted during coating optimization as Hardness range is established during optimization. The risk is reduced to **Low.**
Hardness	Appearance	Low	Tablet appearance and weight gain are not impacted by studied hardness range. The risk is reduced to **Low**.
	Weight gain	Low	
Solid content	Appearance	Low	Solid content of the dispersions was optimized. Excellent tablet appearance was found with selected dispersion. The risk is deduced to **Low.**
	Weight gain	Low	
Inlet Air Temp. (ºC)	Appearance	Low	During coating stage optimization, different level of Inlet air temperature was studied and found good tablet appearance with inlet air temperature > 50°C. The risk is reduced to **Low.**
	Weight gain	Low	Standard weight gain was showed with variation of inlet air temperature. Therefore, risk of weight gain is mitigated. The risk is reduced to **Low.**
	Degradation Products	Low	From coating stage optimization, it is evident that degradation product is not impacted by inlet air temperature range (50-70°C) proposed for coating operations. The risk is reduced to **Low**.
	Appearance	Low	Risk of this step is optimized at lab and exhibit scale. However, this step to be controlled at commercial manufacturing in respect to the

Variables	**Output Material Attributes**	**Risk Category**	**Justification**
Inlet Air Volume (CFM)	Weight gain	Low	intended equipment. The level of risk is reduced to **Low** from the initial risk assessment.
Atomizing Air Pressure (AAP)	Appearance	Low	Atomizing Air Pressure is optimized during development and same is proposed for commercial operations. The risk is reduced to **Low.**
	Weight gain	Low	
	Dissolution	Low	
Spray Rate (RPM)	Appearance	Medium	Spray Rate has impact on tablet appearance. Spray rate is optimized at lab scale but during scale up spray rate need to be verified based pan size, pan load and inlet air volume. The level of risk is reduced from **High** to **Medium.**
	Weight gain	Low	Weight gain range established during formulation development and controlled in batch record. The risk is reduced to **Low.**
	Dissolution	Low	Weight gain range is optimized at lab and exhibit scale. However, this step to be verified at commercial manufacturing in respect to the intended equipment. The risk is reduced to **Low.**
	Degradation Products	Low	
Pan Speed (RPM)	Appearance	Medium	Risk of this step is optimized at lab and exhibit scale. However, this step to be verified at commercial manufacturing in respect to the intended equipment. The level of risk is not reduced from the initial risk assessment
	Weight gain	Medium	

2.2.4 Process Scale up

2.2.4.1 Scale up batch manufacturing strategy

Scale up batch of Atorvastatin Calcium Tablets USP 10 mg, 20 mg, 40 mg and 80 mg manufactured at pilot plant utilizing the equipment, manufacturing process and raw materials intended for proposed exhibit batches manufacturing to verify the potential critical process parameters identified at laboratory scale.

The batch size was 56.000 kg for common blend (Atorvastatin calcium Tablets USP 10 mg, 20 mg, 40 mg and 80 mg; Ref. BMR: BMR/TT/0060022) from where,

- 7.124 kg (equivalent to 49,565 Tablets) for 10 mg strength were compressed and coated (Ref. BMR: BMR/TT/0060026),
- 7.188 kg (equivalent to 25,000 Tablets) for 20 mg strength were compressed and coated (Ref. BMR: BMR/TT/0060025),
- 7.188 kg (equivalent to 12,500 Tablets) for 40 mg strength were compressed and coated (Ref. BMR: BMR/TT/0060024),
- 34.500 kg (equivalent to 30,000 Tablets) for 80 mg strength were compressed and coated (Ref. BMR: BMR/TT/0060023).

The raw materials used in the manufacturing process were purchased from approved suppliers and its approval status verified by QA personnel before commencing the dispensing activities. Respective personnel issued the indented raw materials for each stages of manufacturing and it was counter checked by production personnel and verified by QA. The major equipment was used during manufacturing of scale up batch are presented below Table 106 and details of raw materials used are enclosed in Table 107.

Table 106: Major Equipment used for Manufacturing of Scale-up of Atorvastatin calcium Tablets USP, 10 mg, 20 mg, 40 mg & 80 mg.

S/N	Equipment/ Instrument Name	Equipment/ Instrument ID No.	Capacity	Make
1.	Vibratory sifter	AHL-1-TT-E-18-031	N/A	Russell Finex Sieves and Filters Pvt. Ltd.
2.	Fluid Bed Processor (FBP)	AHL-1-TT-E-16-004	362 L	Glatt Systems Pvt. Ltd.
3.	Co-Mill	AHL-1-TT-E-16-005	N/A	Glatt Systems Pvt. Ltd.
4.	Bin-Blender	AHL-1-TT-E-16-006	400 L	Nantong Beite Pharmaceutical Machinery co. Ltd.
5.	Compression Machine	AHL-1-TT-E-16-033	16 Station Single Rotary Compression Machine	Luxner (kg Pharma)
6.	Coating Machine	AHL-1-TT-E-16-012	56 L	Glatt Systems Pvt. Ltd.

Table 107: Raw Materials Details and Composition used for Manufacturing of Scale up of Atorvastatin calcium Tablets USP, 10 mg, 20 mg, 40 mg & 80 mg

S/N	Ingredients	Amount (mg/ Tablet)				(% w/w to the core tablet)
		80 mg	40 mg	20 mg	10 mg	
Intra-granular						
1	Atorvastatin Calcium Trihydrate[1]	86.6000	43.3000	21.6500	10.8250	7.241
2	Precipitated Calcium Carbonate (Sturcal L)	258.7500	129.3750	64.6875	32.3438	21.635
3	Microcrystalline Cellulose (Vivapur 301)[2]	439.7750	219.8875	109.9437	54.9719	36.770
4	Lactose Monohydrate (Pharmatose 200M)	270.0000	135.0000	67.5000	33.750	22.575
5	Sodium Starch Glycolate Type A (Primojel®)	28.7500	14.3750	7.1875	3.5938	2.404
Binder Solution						
6	Hydroxy Propyl Cellulose (Klucel EF Pharm)	25.8750	12.9375	6.4688	3.2344	2.163
7	Polysorbate 80 (Kolliphor PS 80)	2.8750	1.4375	0.7188	0.3594	0.240
8	Purified Water@	QS	QS	QS	QS	N/A
Extra-granular						
9	Croscarmellose Sodium (Ac-Di-Sol® SD-711)	28.7500	14.3750	7.1875	3.5938	2.404
10	Magnesium Stearate (Veg.)	8.6250	4.3125	2.1563	1.0781	0.721
	Total weight of core tablet (mg)	**1150.000**	**575.000**	**287.500**	**143.750**	N/A
Film Coating (Step I)						
11	Opadry II Complete Film Coating System (White; 85F18422)	40.2500	20.1250	10.0625	5.0313	3.365
12	Hypromellose 2910, 6 mPa.s	2.8750	1.4375	0.7188	0.3594	0.240
13	Purified Water@	QS	QS	QS	QS	N/A
Film Coating (Step II)						
14	Opadry® Complete Film Coating System ((Clear; YS-1R-7006)	2.8750	1.4375	0.7188	0.3594	0.240
15	Purified Water@	QS	QS	QS	QS	N/A
	Total weight of coated tablet (mg)	**1196.000**	**598.000**	**299.000**	**149.499**	**100.000**

@Not part of final product as it is eliminated during drying.

Note:

1. Calculate and dispense the Atorvastatin Calcium Trihydrate USP based on the 100% w/w assay on anhydrous basis and nil % of water content.
2. Adjust the quantity of Microcrystalline Cellulose based on the actual quantity of Atorvastatin Calcium Trihydrate USP taken, to maintain the constant tablet weight.

2.2.4.2 Narrative Summary of Manufacturing Process:

Dispensing:

Weigh all the ingredients for the batch and pack each in double lined polythene bag with proper label.

Sifting, Premixing & Granulation:

1. Co-Sift Atorvastatin Calcium Trihydrate USP & Calcium Carbonate through mesh #20 using vibratory sifter and collect into polybag.
2. Sift Sodium Starch Glycolate, Microcrystalline Cellulose & Lactose Monohydrate through mesh #20 using vibratory sifter.
3. Perform premixing using Bin-Blender (400L) and mix for 10 minutes at 10±1 RPM.
4. Prepare binder solution using Hydroxy Propyl Cellulose (Klucel EF) and Polysorbate 80 in purified water for top spray granulation.
5. Perform top spray granulation at Fluid Bed Processor and continue drying after completion of spraying to get LOD range 1.20-2.00 % (measured at 105°C in auto mode).
6. Sieve the dried granules through mesh #20 using vibratory sifter & mill the retain granules through 1.2 mm using Co-mill.

Blending & Lubrication:

7. Sift Croscarmellose Sodium through mesh #40 using vibratory sifter.
8. Take the size reduction granules & sifted croscarmellose sodium into Bin-blender and perform blending at Bin-Blender (400 L) for 10 minutes at 10±1 RPM
9. Sift magnesium stearate through mesh #40 using vibratory sifter. Transfer the sifted magnesium stearate into Bin-Blender (400 L) and perform lubrication for 5 minutes at 10±1 RPM

Compression:

Compress the blend into 10 mg, 20 mg, 40 mg and 80 mg strengths using suitable compression tooling.

Coating:

Coat the compressed tablets using suitable coating pan in coating machine

2.2.4.3 Yield Range of Scale up batch

The Permissible yield range for different unit operations of scale up batch provided in Table 108.

Table 108: Permissible Yield Range for Different Unit Operations of Scale up Batch

S/N	Stage		Results				Limit
1	**MILLED GRANULES**	Stage yield	94.32 %				90.00 - 100.00 %
		Overall yield	96.52 %				95.00 - 100.00 %
2	**BLENDING**	Stage yield	93.79 %				90.00 - 100.00 %
		Overall yield	94.35 %*				95.00 - 100.00 %
			10 mg	**20 mg**	**40 mg**	**80 mg**	
3	**Compression**	Stage yield	87.13 %*	86.05 %*	82.[illegible]8 %*	90.48 %	90.00 - 100.00%
		Overall yield	97.98 %	97.82 %	98.29 %	99.73 %	95.00 - 100.00%
4	**Coating**	Stage yield	97.36 %	98.4[illegible] %	90.34 %	95.20 %	90.00 - 100.00%
		Overall yield	99.05 %	101.12%*	98.21 %	97.55 %	95.00 - 100.00%
*** will be finalized after completion of validation batches.**							

2.2.4.4 Critical Quality Parameter and Data for Scale up batch

2.2.4.4.2 Stage: After Lubrication

Table 109: Blend Uniformity of the Samples Collected from Bin-Blender (after Blending and Lubrication) and from SS Vessel (after unloading)

Measured Parameter	**Blend uniformity**	**Acceptance Criteria**	**Assay value should not be less than 90.0 % and not more than 110.0 % , RSD: NMT 5.0 %**
Sampling Location		**After lubrication from Bin-Blender & SS Vessel**	
Sample No.	**Bin Blender**		**SS Vessel**
1	96.6 %		94.2 %
2	99.0 %		95.8 %
3	95.8 %		95.2 %
4	95.9 %		95.1 %
5	95.0 %		96.3 %
6	95.4 %		95.8 %
7	96.0 %		95.7 %
8	99.4 %		96.9 %

<table>
<tr><th>Measured Parameter</th><th>Blend uniformity</th><th>Acceptance Criteria</th><th>Assay value should not be less than 90.0 % and not more than 110.0 % , RSD: NMT 5.0 %</th></tr>
<tr><th colspan="2">Sampling Location</th><th colspan="2">After lubrication from Bin-Blender & SS Vessel</th></tr>
<tr><td>9</td><td colspan="2">96.5 %</td><td>95.4 %</td></tr>
<tr><td>10</td><td colspan="2">96.0 %</td><td>97.4 %</td></tr>
<tr><td>Minimum</td><td colspan="2">95.0 %</td><td>94.2 %</td></tr>
<tr><td>Maximum</td><td colspan="2">99.4 %</td><td>97.4 %</td></tr>
<tr><td>Average %</td><td colspan="2">96.2</td><td>95.8</td></tr>
<tr><td>RSD %</td><td colspan="2">1.1</td><td>0.9</td></tr>
<tr><td>A.R. No.</td><td colspan="2">202283</td><td>202284</td></tr>
</table>

Note: 10 samples (In triplicate) collected from Bin Blender (After Lubrication) and SS Vessel (After unloading the lubricated blend).

1X to 3X , where X= 143.750 mg

Table 110: Results of Pooled Sample at Blending and Lubrication Stage

S/N	TESTS	SPECIFICATION		Results
1	Description	White to off white powder		Complies
2	Loss on drying at 105°C	Not more than 3.5 % w/w		2.1 %
3	Blend Uniformity	**Stage -1:** RSD of all individual results should be not more than 5.0 %. Mean of all results should be 90.0 % to 110.0 % of target assay. All individual results should be within 10.0 % (absolute*) of the mean of the results. **Stage -2:** RSD of all individual results should be not more than 6.0 %. Mean of all results should be 90.0 % to 110.0 % of target assay. All individual results should be within the range of 85.0 % to 115.0 % of target strength.		Min: 94.2 % Max: 97.4 % Avg: 95.8 % RSD: 0.9
4	Assay by HPLC	Not less than 94.5% w/w and Not more than 105.0% w/w of the labeled amount of Atorvastatin.		97.1 %
5	Sieve analysis (Retained %)	For information only	#60	0.3 %
			#100	3.5 %
			#200	53.7 %
6	Bulk density	For information only		0.4 g/ml
7	Tapped density	For information only		0.5 g/ml
8	Carr's index	For information only		15.08 %
9	Hausner's Ratio	For information only		1.2
A.R. No.				**202282**

2.2.4.4.3 Stage: Compression

Table 111: Content uniformity at Compression Stage of Scale up Batch

Measured Parameter: Content uniformity (%)					**Acceptance Criteria:** Meets the requirement of USP <905> Acceptance value NMT or equal to L1 (L1 is 15)							
Stage: Compression: Slow, Medium, Fast												
Tablet No.	**Slow (15 RPM)**				**Medium (20 RPM)**				**Fast (25 RPM)**			
	10 mg	**20 mg**	**40 mg**	**80 mg**	**10 mg**	**20 mg**	**40 mg**	**80 mg**	**10 mg**	**20 mg**	**40 mg**	**80 mg**
Tablet - 1	98.6	99.4	98.5	99.5	98.9	97.8	99.3	98.6	99.9	97.7	100.0	99.7
Tablet - 2	98.1	98.4	98.6	99.3	98.3	96.5	99.3	98.8	98.4	96.6	99.4	98.4
Tablet - 3	98.2	97.7	99.6	99.1	97.5	99.1	98.7	99.6	98.5	98.9	100.6	99.0
Tablet - 4	98.6	98.6	99.7	101.1	99.3	98.5	99.7	100.4	98.5	96.3	99.6	99.4
Tablet - 5	97.9	98.5	99.2	99.2	98.2	97.2	98.9	98.6	98.1	97.8	98.3	99.0
Tablet - 6	98.7	97.8	99.6	98.7	98.7	98.8	99.6	99.4	98.0	98.6	98.5	100.0
Tablet - 7	98.6	98.8	99.4	99.2	97.6	100.0	99.3	99.7	98.9	97.7	98.3	98.9
Tablet - 8	98.6	97.9	99.1	99.1	98.4	99.2	99.4	99.2	97.7	100.6	99.6	99.6
Tablet - 9	97.9	98.3	99.0	100.0	97.4	98.3	99.0	98.8	98.1	99.2	98.9	98.7
Tablet - 10	98.0	97.6	99.4	97.8	97.9	97.5	98.6	99.9	98.3	99.5	98.7	100.1
Minimum	**97.9**	**97.6**	**98.5**	**97.8**	**97.4**	**96.5**	**98.6**	**98.6**	**97.7**	**96.3**	**98.3**	**98.4**
Maximum	**98.7**	**99.4**	**99.7**	**101.1**	**99.3**	**100.0**	**99.7**	**100.4**	**99.9**	**100.6**	**100.6**	**100.1**
Average (%)	**98.3**	**98.3**	**99.3**	**99.3**	**98.3**	**98.3**	**99.2**	**99.3**	**98.3**	**98.3**	**99.2**	**99.3**
SD (%)	**0.61**	**0.55**	**0.41**	**0.84**	**0.56**	**1.04**	**0.36**	**0.61**	**0.38**	**1.32**	**0.78**	**0.56**
Acceptance value	**1.0**	**1.5**	**1.0**	**2.0**	**1.5**	**2.7**	**0.9**	**1.5**	**1.1**	**3.4**	**1.9**	**1.3**
A.R. No.	**202588**	**202603**	**202609**	**202777**	**202587**	**202607**	**202610**	**202776**	**202586**	**202606**	**202611**	**202775**

Table 112: Content uniformity at Compression Stage of Scale up Batch

Measured Parameter: Content (%)					**Acceptance Criteria:** Meets the requirement of USP <905> Acceptance value NMT or equal to L1 (L1 is 15)							
Stage: Compression: Initial, Middle, End												
Tablet No.	**Initial**				**Middle**				**End**			
	10 mg	**20 mg**	**40 mg**	**80 mg**	**10 mg**	**20 mg**	**40 mg**	**80 mg**	**10 mg**	**20 mg**	**40 mg**	**80 mg**
Tablet - 1	98.9	97.7	99.1	99.1	97.8	97.7	98.8	99.3	98.1	99.3	99.4	99.7
Tablet - 2	98.6	97.4	99.3	98.7	99.2	96.4	98.9	99.1	99.1	97.8	99.2	99.9
Tablet - 3	98.0	99.5	98.9	98.7	98.6	98.6	99.5	99.2	98.8	98.4	98.8	99.2
Tablet - 4	98.2	99.1	99.0	98.4	97.2	99.3	99.5	98.5	99.5	97.0	99.3	99.8
Tablet - 5	98.8	97.7	98.9	99.6	98.8	97.8	98.9	99.2	97.4	98.9	98.7	99.9
Tablet - 6	97.7	100.2	99.2	98.8	98.5	97.7	99.4	99.6	98.4	97.7	99.8	99.2
Tablet - 7	98.6	98.5	99.3	100.7	98.5	99.1	98.9	99.1	97.3	98.3	98.8	99.0
Tablet - 8	97.2	97.7	99.5	99.4	97.8	98.0	98.9	100.2	97.5	99.0	99.0	98.5
Tablet - 9	98.7	97.3	99.3	99.3	98.6	99.0	99.7	99.1	97.5	96.8	99.2	98.9
Tablet - 10	98.4	97.9	99.5	100.3	98.0	99.5	99.5	99.3	99.4	99.7	99.6	98.8
Minimum	**97.2**	**97.3**	**98.9**	**98.4**	**97.2**	**96.4**	**98.8**	**98.5**	**97.3**	**96.8**	**98.7**	**98.5**
Maximum	**98.9**	**100.2**	**99.5**	**100.7**	**99.2**	**99.5**	**99.7**	**100.2**	**99.5**	**99.7**	**99.8**	**99.9**
Average (%)	**98.3**	**98.3**	**99.2**	**99.3**	**98.3**	**98.3**	**99.2**	**99.3**	**98.3**	**98.3**	**99.2**	**99.3**
SD (%)	**0.54**	**0.98**	**0.23**	**0.72**	**0.61**	**0.96**	**0.33**	**0.45**	**0.86**	**0.95**	**0.37**	**0.51**
Acceptance value	**1.5**	**2.6**	**0.6**	**1.7**	**1.7**	**2.5**	**0.8**	**1.1**	**2.3**	**2.5**	**0.9**	**1.2**
A.R No.	**202596**	**202597**	**202617**	**202788**	**202595**	**202598**	**202618**	**202787**	**202594**	**202599**	**202619**	**202786**

Table 113: Results of different physical parameters at compression stage for scale up batch

Atorvastatin Calcium Tablets USP, 80 mg								
Slow (15 RPM)	Uniformity of Weight of 20 Tablet (mg): 1150.000 mg ± 5.00 % (1092.500–1207.500) mg	1140.700	Group weight of 20 tablets (mg): 23.00 g ± 3.0 % (22.310–23.690) g	23.030 g	Hardness (kp): (18-26) kp Target- 22.0 kp	20.93	Thickness (mm): 7.10 mm ± 0.40 (6.70-7.50) mm	7.06
		1160.550				24.29		7.11
		1151.485				22.68		7.09
Medium (20 RPM)		1141.700		23.030 g		18.29		7.06
		1162.890				23.13		7.14
		1151.167				21.10		7.10
Fast (25 RPM)		1125.060		22.965 g		18.87		7.08
		1164.770				22.78		7.16
		1148.233				21.01		7.12
Atorvastatin Calcium Tablets USP, 40 mg								
Slow (15 RPM)	Uniformity of Weight of 20 Tablet (mg) 575.000 mg ± 5.00 % (546.250–603.750) mg	569.780	Group weight of 20 tablets (mg) 11.500 g ± 3.0 % (11.155–11.845) g	11.508 g	Hardness (kp) (13-21) kp Target- 17.0 kp	16.34	Thickness (mm) 5.40 mm ± 0.40 (5.00-5.80) mm	5.28
		578.990				18.22		5.29
		575.387				17.23		5.29
Medium (20 RPM)		571.750		11.521 g		14.28		5.28
		582.340				17.88		5.31
		576.063				16.68		5.30
Fast (25 RPM)		564.840		11.455 g		14.24		5.28
		580.930				17.43		5.32
		572.759				15.80		5.31
Atorvastatin Calcium Tablets USP, 20 mg								
Slow (20 RPM)	Uniformity of Weight of 20 Tablet (mg) 287.500 mg ± 7.5 % (265.938–309.063) mg	284.500	Group weight of 20 tablets (mg) 5.750 g ± 5.0 % (5.463–3.038) g	5.762 g	Hardness (kp) (6-14) kp Target- 10.0 kp	12.99	Thickness (mm) 3.30 mm ± 0.40 (2.90-3.70) mm	4.34
		292.510				15.14		4.40
		288.195				14.14		4.37
Medium (25 RPM)		287.290		5.863 g		12.50		4.36
		296.800				14.60		4.42
		293.190				13.63		4.40
Fast (30 RPM)		280.300		5.736 g		12.27		4.36
		293.500				15.66		4.40
		286.791				13.87		4.38
Atorvastatin Calcium Tablets USP, 10 mg								
Slow (20 RPM)	Uniformity of Weight of 20 Tablet (mg) 143.750 mg ± 7.5 % (132.969–154.531) mg	141.930	Group weight of 20 tablets (mg) 2.875 g ± 5.0 % (2.731–3.019) g	2.879 g	Hardness (kp) (6-14) kp Target- 10.0 kp	9.48	Thickness (mm) 3.30 mm ± 0.40 (2.90-3.70) mm	3.29
		145.980				10.67		3.32
		143.967				10.03		3.30
Medium (30 RPM)		142.780		2.883 g		9.63		3.27
		145.660				10.47		3.31
		144.170				10.10		3.30
Fast (40 RPM)		142.850		2.883 g		9.32		3.28
		145.720				10.29		3.32
		144.142				9.77		3.30

Table 114: Drug Release at Compression Stage of Scale up Batch at High Hardness and Low Hardness

Test Conditions	USP type -2 apparatus, 900 mL,0.06 N Hydrochloric acid (medium), 50 RPM, 37 °C
Acceptance Criteria	Not less than 80% (Q) of the labeled amount of Atorvastatin is dissolved in 30 minutes.

Tablet No.	**Low hardness**				**High Hardness**			
	10 mg	**20 mg**	**40 mg**	**80 mg**	**10 mg**	**20 mg**	**40 mg**	**80 mg**
Tablet - 1	100	101	99	99	101	103	98	96
Tablet - 2	100	97	97	95	97	97	97	99
Tablet - 3	96	97	98	97	97	99	97	97
Tablet - 4	96	99	97	97	98	96	96	99
Tablet - 5	98	97	96	98	96	97	98	98
Tablet - 6	96	97	98	99	101	96	96	97
Minimum	**96**	**97**	**96**	**95**	**96**	**96**	**96**	**96**
Maximum	**100**	**101**	**99**	**99**	**101**	**103**	**98**	**99**
Average (%)	**98**	**98**	**98**	**98**	**98**	**98**	**97**	**98**
A.R. No.	**202589**	**202604**	**202615**	**202774**	**202590**	**202605**	**202616**	**202773**

Table 115: In-process CQAs for Pooled Samples at Compression Stage of Scale up Batch

Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg						
S/N	**Parameter**	**Acceptance Criteria**	**10 mg**	**20 mg**	**40 mg**	**80 mg**
1	Content uniformity	Meets the requirement in USP NF <905> Acceptance value ≤ 15.0	Min: 96.6 Max: 100.0 Avg: 98.1 AV: 3.5	Min: 97.1 Max: 99.2 Avg: 98.0 AV: 2.2	Min: 97.2 Max: 100.1 Avg: 98.8 AV: 2.2	Min: 99.3 Max: 101.9 Avg: 100.8 AV: 2.3
2	Assay (By HPLC)	Not less than 94.5% and not more than 105.0% of the labeled amount	98.3	98.3	99.2	99.3
3	Dissolution	Not less than 80% (Q) of the labeled amount of Atorvastatin is dissolved in 30 minutes.	Min: 89 Max: 95 Avg: 91	Min: 93 Max: 94 Avg: 93	Min: 98 Max: 100 Avg: 99	Min: 96 Max: 103 Avg: 98
A.R. No.			**202580**	**202581**	**202608**	**202785**

Table 116: Results for Pooled Samples at Coating Stage of Scale-up Batch

Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg						
S/N	**Parameter**	**Acceptance Criteria**	**10 mg**	**20 mg**	**40 mg**	**80 mg**
1	Description	**10 mg:** A White to off white colored, film-coated, oval shaped, unscored tablets with "AHI" debossed on one side and "10" on the other side.	Complies	Complies	Complies	Complies
		20 mg: A White to off white colored, film-coated, oval shaped, unscored tablets with "AHI" debossed on one side and "20" on the other side.				
		40 mg: A White to off white colored, film-coated, oval shaped, unscored tablets with "AHI" debossed on one side and "40" on the other side.				
		80 mg: A White to off white colored, film-coated, oval shaped, unscored tablets with "AHI" debossed on one side and "80" on the other side.				
2	Identification A. By UV	The UV absorption spectrum of the major peak of the sample solution corresponds to that of the standard solution, as obtained in the assay.	Complies	Complies	Complies	Complies
	Identification B. By HPLC	The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in	Complies	Complies	Complies	Complies
3	Water content by KF	Not more than 6.0 % w/w	4.0	5.80	3.6	3.7
4	Uniformity of dosage units (by content uniformity)	Meets the requirement in USP NF <905> Acceptance value (AV) ≤ 15.0	AV: 1.9	AV: 1.6	AV: 1.0	AV: 2.5
5	Assay (By HPLC)	Not less than 94.5% and not more than 105.0% of the labeled amount	99.4	99.2	97.4	99.7
6	Organic Impurities by HPLC					

Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg

S/N	Parameter	Acceptance Criteria	10 mg	20 mg	40 mg	80 mg
6.1	Atorvastatin pyrrolidone analog	Not more than 0.5 %	0.1	0.0	0.0	0.1
6.2	Atorvastatin related compound H	Not more than 1.0 %	0.0	ND	0.0	0.0
6.3	Atorvastatin epoxypyrrolooxazin 6-hydroxy analog	Not more than 0.5 %	ND	ND	ND	ND
6.4	Atorvastatin epoxypyrrolooxazin 7-hydroxy analog	Not more than 0.5 %	ND	0.0	ND	0.1
6.5	Atorvastatin epoxy THF analog & Atorvastatin related Compound D*	Not more than 1.5%	0.2	ND	0.0	0.0
6.6	Any other unspecified degradation product	Not more than 0.2%	0.0	0.2	0.0	0.0
6.7	Total impurities	Not more than 4.0%	0.4	ND	0.2	0.3
7	Dissolution by HPLC	NLT 80% (Q) of the labeled amount of atorvastatin is dissolved in 30 minutes.	Min: 93 Max: 96 Avg: 94	Min: 91 Max: 97 Avg: 93	Min: 97 Max: 99 Avg: 98	Min: 96 Max: 99 Avg: 98
8	Microbial enumeration test and tests for special microorganisms					
8.1	Total viable aerobic microbial count	Not more than 1000 cfu/g	45	45	45	50
8.2	Total combined molds and yeasts count	Not more than 100 cfu/g	<100	<100	<100	<100
8.3	*Escherichia coli*	Absent in 1 g	Absent/g	Absent/g	Absent/g	Absent/g
A.R. No.			**202792, M201068**	**202780, M201075**	**202783, M201076**	**202778, M201084**

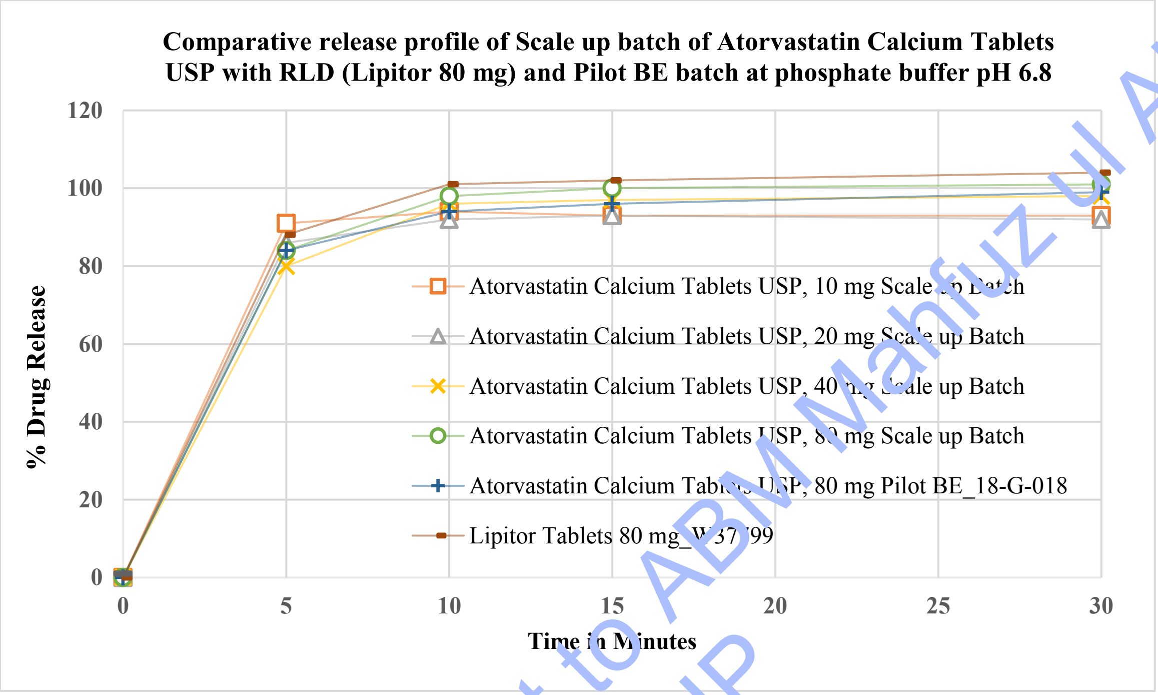

Figure 9: Comparative release profile of Scale up of Atorvastatin Calcium Tablets USP batch with RLD (Lipitor 80 mg) and Pilot BE batch at phosphate buffer pH 6.8

Inference (Scale up batch):

The Scale up batch is manufactured a larger batch size then development batch so that the potential problems of scale-up can be addressed, as they arise with larger size manufacturing equipment that use the same operating principle. The intermediate (in process) CQAs of the output material from each process step that could impact the final drug product CQAs were identified and tested. to ensure that scale-up will not affect quality and/or efficacy. The results of the scale up batch indicates that the process parameters controlled at each unit operations are suitable to meet the in process CQAs of each step and final drug product CQAs.

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2.2.5 Updated Risk Assessment of the Drug Product Manufacturing Process

During process development, the identified high risks for each process steps are addressed. Experimental studies are defined and executed in order to establish additional scientific knowledge and understanding to allow appropriate controls to be developed and implemented, and to reduce the risk to an acceptable level. After detailed experimentation, the initial manufacturing process risk assessment was updated to be in line with the current process understanding. Table 117 describes how the application of the control strategy to the manufacturing process has been reduced the identified risks. Table 118 provides the justification for the reduced risk following process development.

Table 117: Updated Risk Assessment of the Manufacturing Process on Drug Product CQAs

Drug product CQAs	**Manufacturing Process Steps**						
	Co-Sifting & Sifting	**Pre-Mixing**	**Top Spray Granulation**	**Blending and Lubrication**	**Compression**	**Coating**	**Packaging**
Assay	Low*	Low*	Medium*	Low*	Low*	Low	Low
Content uniformity	Low*	Low*	Medium*	Low*	Medium*	Low	Low
Dissolution	Low	Low	Low*	Low*	Low*	Low*	Low
Degradation Products	Low*	Low	Low	Low	Low	Low*	Low*

***The level of risk is reduced from the initial risk assessment.**

Table 118: Justification of Updated Risk Assessment of the Manufacturing Process on Drug Product CQAs

Process Steps	**Drug Product CQAs**	**Risk Category**	**Justification**
Co-Sifting & Sifting	Assay	Low	During co-sifting drug substance is mixed with calcium carbonate at vibratory sifter and rest of the excipients mixing sequentially. At adopted co sifting process, predefined quality attributes met for the intermediate (in process) CQAs of the output material from each process step and final drug product CQAs. The risk is reduced to **Low**.
	Content uniformity	Low	
	Degradation Products	Low	
Pre-Mixing	Assay	Low	At adopted pre-mixing process, predefined quality attributes met for the intermediate (in process) CQAs of the output material from each process step and final drug product CQAs. The risk is reduced to **Low**.
	Content uniformity	Low	
Top Spray Granulation	Assay	Medium	Under or over granulation may produce unequal granules which may impact content uniformity/weight variation which is optimized at lab and exhibit scale. However, this step to be verified at commercial manufacturing in respect to the intended equipment. The level of risk is reduced from **High to Medium** from the initial risk assessment.
	Content uniformity	Medium	
	Dissolution	Low	Top spray granulation stage did not exhibit a significant impact on dissolution and degradation products of the tablets. The risk is reduced to **Low.**
	Degradation Products	Low	
Blending and Lubrication	Assay	Low	The granule uniformity which affects content uniformity is controlled by earlier steps. This step is to blend the granules with small quantities of extra granular excipients. Blending and lubrication steps optimized and found not critical. The risk reduced to **Low.**
	Content uniformity	Low	
	Dissolution	Low	Number of revolutions and magnesium stearate specific surface area did not exhibit a significant impact on dissolution of the tablets. The risk is reduced to **Low.**
Compression	Assay	Low	Process parameter optimized lab and scale up stage and found less impacting to the tablet assay. The risk reduced to **Low.**
	Content uniformity	Medium	Compression process variables can cause tablet weight variability which could cause tablets to fall out-of-specification for content uniformity. Process parameter optimized lab and scale up stage. However, this step to be further verified in the intended equipment at commercial manufacturing. The risk is reduced to **Medium.**
	Dissolution	Low	Within the optimized hardness range, compression process parameters have no impact on dissolution of the dosage form. The risk reduced to **Low.**

Coating	Dissolution	Low	Within standard weight gain (3.0-5.0) % for Atorvastatin calcium Tablets USP meet predefined criteria of dissolution. The risk reduced to **Low.**
	Degradation Products	Low	Opadry II White (85F18422) and Hypromellose 2910, 6 mPa.s (Pharmacoat 606) were selected as ready mix coating material to provide moisture barrier coat. Therefore, the risk is reduced to **Low.**
Packaging	Degradation Products	Low	HDPE container and closure with appropriate desiccant was selected to provide protection from environmental factors i.e. auto oxidation. Stability data of prototype batch meet predefined criteria for Assay and degradation products. The risk is reduced to **Low.**

Based on process optimization summary results, critical process product parameters were established for scale-up and exhibit batches. The same process parameters will be validated during validation campaign for commercialization.

2.2.6 Process Scale up Summary

Table 119: Process Scale up summary

Scale	Batch Size (kg)	Units (No. of tablet)
Lab Batch	5.000 kg Common Blend	For 10 mg strength: 5,925 Tablets For 20 mg strength: 3,838 Tablets For 40 mg strength: 2,435 Tablets For 80 mg strength: 1,220 Tablets
Scale up (Eng.) Batch	56.000 kg Common Blend	For 10 mg strength: 49,565 Tablets For 20 mg strength: 25,000 Tablets For 40 mg strength: 12,500 Tablets For 80 mg strength: 30,000 Tablets
Exhibit Batch	280.313 kg Common Blend	For 10 mg strength: 180,000 Tablets For 20 mg strength: 135,000 Tablets For 40 mg strength: 135,000 Tablets For 80 mg strength: 120,000 Tablets
Commercial (Proposed)	For 10 mg strength: 258.750 kg For 20 mg strength: 388.125 kg For 40 mg strength: 471.500 kg For 80 mg strength: 471.500 kg	For 10 mg strength: 1,800,000 Tablets For 20 mg strength: 1,350,000 Tablets For 40 mg strength: 820,000 Tablets For 80 mg strength: 410,000 Tablets

Based on experience on wet granulation process, top spray granulation, blending, compression and coating stage are considered as critical for robust manufacturing process. During scale up, lab scale to semi scale up and exhibit scale, similar granulation parameter and predefined hardness range are considered critical to meet batch to batch consistency.

To scale-up the blending and lubrication process, same number of revolutions and similar blender fill volume were maintained from lab to exhibit batch and upon approval to commercial batch. During formulation development, compression process development and optimization summary lab model compression machine was used.

A scale up batch was designed for granulation and compression process development with equipment that were used at exhibit batch. All process parameter was evaluated to meet intermediate CQAs and drug product CQAs.

2.3 Exhibit Batch Manufacturing

Based on the knowledge gained during Lab scale-up batch manufacturing, same principles were used for manufacturing of the exhibit batch of Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg. Three batches of 280.313 kg (Common Blend) were manufactured for each strength using two lot of API (Lot # 3141900140 and Lot # 3141900141). Both the API lot was used in Pivotal BE batch preparation.

Table 120: Exhibit Batch Manufacturing Formula for Atorvastatin Calcium Tablets USP

S/N	**Ingredients**	**Amount (mg/ Tablet)**				**(% w/w to the core tablet)**
		80 mg	**40 mg**	**20 mg**	**10 mg**	
Intra-granular						
1	Atorvastatin Calcium Trihydrate[(1)]	86.6000	43.3000	21.6500	10.8250	7.241
2	Precipitated Calcium Carbonate (Sturcal L)	258.7500	129.3750	64.6875	32.3438	21.635
3	Microcrystalline Cellulose (Vivapur 301)[(2)]	439.7750	219.8875	109.9437	54.9719	36.770
4	Lactose Monohydrate (Pharmatose 200M)	270.0000	135.0000	67.5000	33.750	22.575
5	Sodium Starch Glycolate Type A (Primojel®)	28.7500	14.3750	7.1875	3.5938	2.404
Binder Solution						
6	Hydroxy Propyl Cellulose (Klucel EF Pharm)	25.8750	12.9375	6.4688	3.2344	2.163
7	Polysorbate 80 (Kolliphor PS 80)	2.8750	1.4375	0.7188	0.3594	0.240
8	Purified Water@	QS	QS	QS	QS	N/A
Extra-granular						
9	Croscarmellose Sodium (Ac-Di-Sol® SD-711)	28.7500	14.3750	7.1875	3.5938	2.404
10	Magnesium Stearate (Veg.)	8.6250	4.3125	2.1563	1.0781	0.721
Total weight of core tablet (mg)		**1150.000**	**575.000**	**287.500**	**143.750**	N/A
Film Coating (Step I)						
11	Opadry II Complete Film Coating System (White; 85F18422)	40.2500	20.1250	10.0625	5.0313	3.365
12	Hypromellose 2910, 6 mPa.s	2.8750	1.4375	0.7188	0.3594	0.240
13	Purified Water@	QS	QS	QS	QS	N/A
Film Coating (Step II)						
14	Opadry® Complete Film Coating System ((Clear; YS-1R-7006)	2.8750	1.4375	0.7188	0.3594	0.240
15	Purified Water@	QS	QS	QS	QS	N/A
Total weight of coated tablet (mg)		**1196.000**	**598.000**	**299.000**	**149.499**	**100.000**

@Not part of final product as it is eliminated during drying.

Note:

1. Calculate and dispense the Atorvastatin Calcium Trihydrate USP based on the 100% w/w assay on anhydrous basis and nil % of water content.
2. Adjust the quantity of Microcrystalline Cellulose based on the actual quantity of Atorvastatin Calcium Trihydrate USP taken, to maintain the constant tablet weight.

Narrative Summary of Manufacturing Process:

Dispensing:

Weigh all the ingredients for the batch and pack each in double lined polythene bag with proper label.

Sifting, Premixing & Granulation:

1. Co-Sift Atorvastatin Calcium Trihydrate USP & Calcium Carbonate through mesh #20 using vibratory sifter and collect into polybag.
2. Sift Sodium Starch Glycolate, Microcrystalline Cellulose & Lactose Monohydrate through mesh #20 using vibratory sifter.
3. Perform premixing using Bin Blender.
4. Prepare binder solution for granulation.
5. Perform Granulation at Fluid Bed Processor.
6. Check the LOD of granule at 105ºC (auto mode). LOD range 1.20-2.00 %.
7. Sieve the dried granules through mesh #20 using vibratory sifter & mill the retain granules through 1.2 mm using Co-mill.

Blending & Lubrication:

8. Sift Croscarmellose Sodium through mesh #40 using vibratory sifter.
9. Take the granules & sifted Croscarmellose Sodium into Bin-blender.
10. Perform blending using Bin Blender.
11. Sift Magnesium Stearate through mesh #40 using vibratory sifter.
12. Perform Lubrication using Bin Blender.

Compression:

Compress the blend into 10 mg, 20 mg, 40 mg and 80 mg strengths using suitable compression tooling.

Coating:

Coat the compressed tablets using suitable coating pan in coating machine.

Inspection and Metal detection:

Inspect tablets using manual inspection machine and detect metal by metal detector

Packaging:

Pack the coated tablets in HDPE container with desiccant and closure

Table 121: Equipment and Process Parameters Used For the Exhibit Batch

Process Steps	Equipment and Process Parameters
Sifting	Vibratory Sifter (Russell Finex Sieves and Filters Pvt. Ltd.) Mesh size: # 20 mesh and # 40 mesh
Premixing	Bin Blender (Nantong Beite Pharmaceutical Machinery co. Ltd.) Blending Time Period: 10 minutes at 10±1 RPM
Top Spray Granulation	Fluid Bed Processor (Glatt Systems Pvt. Ltd.) Inlet air temperature set value: 50-70˚C
Drying	Fluid Bed Processor (Glatt Systems Pvt. Ltd.) Inlet air temperature set value: 50-70˚C LOD range 1.20-2.00 % at 105ºC (auto mode).
Size reduction	Vibratory sifter (Russell Finex Sieves and Filters Pvt. Ltd.) Mesh size: #20 mesh Co-mill (Glatt Systems Pvt. Ltd.); Screen size: 1.2 mm
Blending and Lubrication	Bin Blender (Nantong Beite Pharmaceutical Machinery Co.) Blending Time period: 10 min at RPM 10±1 Lubrication Time period: 5 min at RPM-10±1
Compression (10 mg, 20 mg, 40 mg and 80 mg)	Compression Machine (PTK Co. Ltd, KG Pharma)
	10 mg strength • Dimensions- 9.80 × 5.10 mm, oval shaped • Punch Tip (upper) – 9.80 × 5.10 mm, oval shaped, biconcave, "10" embossed. • Punch Tip (lower) - 9.80 × 5.10 mm, oval shaped, biconcave, "AHI'' embossed. • Compression machine speed- (40-60) RPM (Optimum 50 RPM)
	20 mg strength • Dimensions- 12.30 × 6.40 mm, oval shaped • Punch Tip (upper) – 12.30 × 6.40 mm, oval shaped, biconcave, "20" embossed.

Process Steps	Equipment and Process Parameters
	• Punch Tip (lower) - 12.30 × 6.40 mm, oval shaped, biconcave, "AHI'' embossed. • Compression machine speed- (40-60) RPM (Optimum 50 RPM)
	40 mg strength • Dimensions- 15.50 × 8.15 mm, oval shaped • Punch Tip (upper) – 15.50 × 8.15 mm, oval shaped, biconcave, "40" embossed. • Punch Tip (lower) - 15.50 × 8.15 mm, oval shaped, biconcave, "AHI'' embossed. • Compression machine speed- (20-30) RPM (Optimum 25 RPM)
	80 mg strength • Dimensions- 19.30 × 10.35 mm, oval shaped • Punch Tip (upper) – 19.30 × 10.35 mm, oval shaped, biconcave, "80" embossed. • Punch Tip (lower) - 19.30 × 10.35 mm, oval shaped, biconcave, "AHI'' embossed. • Compression machine speed- (15-25) RPM (Optimum 20 RPM)
Coating (10 mg, 20 mg, 40 mg and 80 mg)	**Coating Machine (Glatt Systems PVT. Ltd_50 L)** • Speed of Stainless Steel Coating Pan: Should be 1.5 to 15 RPM. • Atomizing air pressure: Should be between 2.0– 4.0 Bar • Nozzle Size: 1.0 mm • Inlet Temperature: 50-70° C • Peristaltic Pump RPM: 5 to 30 • Distance between each gun: (15 - 25) cm • Spray nozzles position- Should be perpendicular to rolling bed of tablets. • Spray nozzles distance from bed-(10 - 25) cm • Spray rate: 40±30 g/min/gun

Process Flow Diagram and Narrative Summary is given below Figure 10

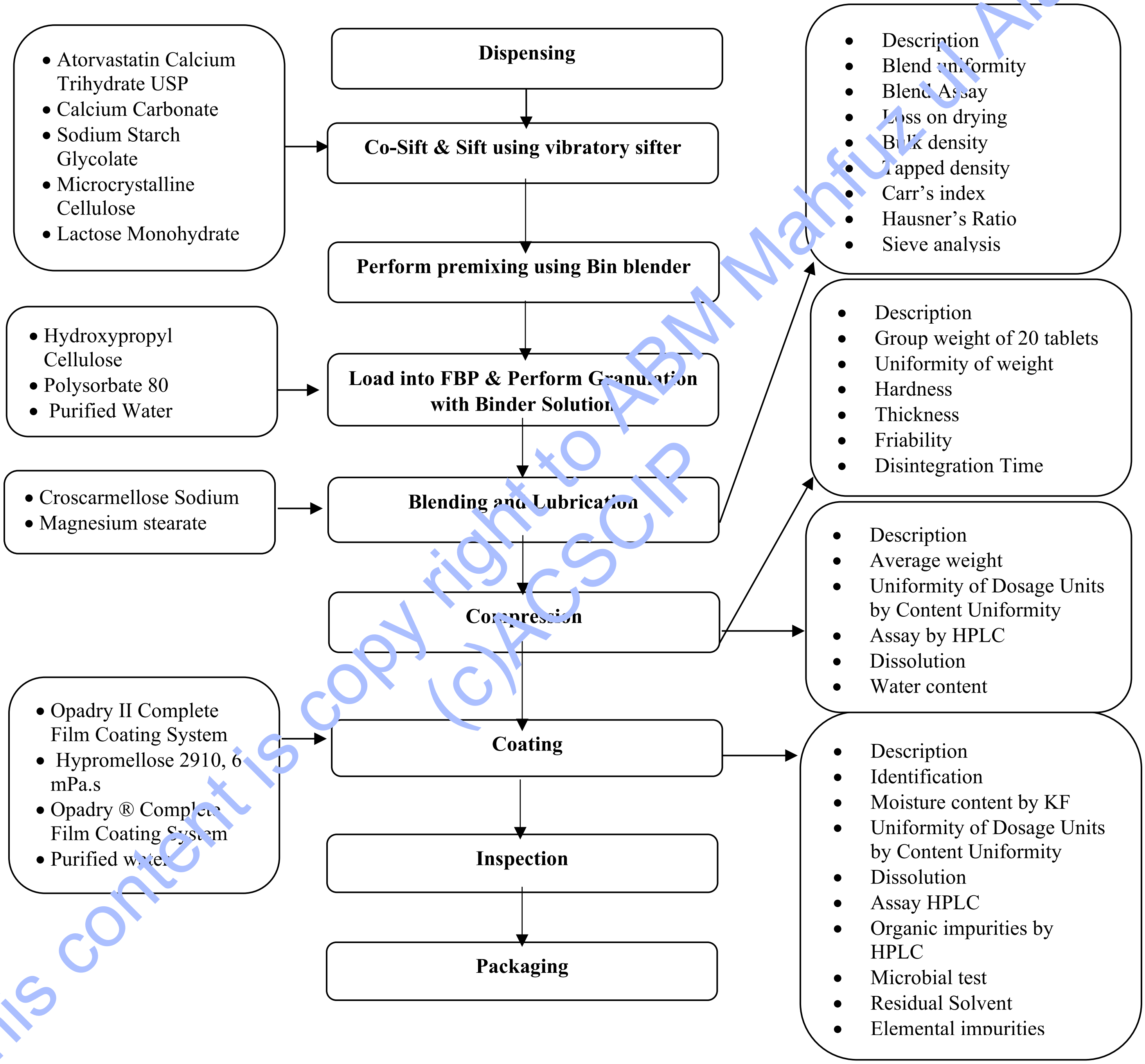

Figure 10: Process flow diagram of Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg.

2.4 Container Closure System

To be consistent with the RLD, the proposed generic drug product is intended to be labeled for Preserve in well-closed containers and store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). The Reference product has chosen cylindrical HDPE bottle with an induction seal liner along with desiccant and child resistant (CR) closure. Generic Atorvastatin Calcium Tablets USP, shall be packaged in round HDPE bottle with an induction seal liner caps and the pack details are described in Table 122.

Table 122: Proposed Commercial Packaging for Generic Atorvastatin Calcium Tablets USP

Strength	Counts	Container	Closure	Cansiter
10 mg	90's count	40 CC HDPE Container	33 mm CR Closure	1 g cansiter
	1000's count	250 CC HDPE Container	53 mm CR Closure	2 g cansiter
	Bulk Pack (5000's)	5L Bucket with lid		(5 X 2) g cansiter
20 mg	90's count	40 CC HDPE Container	33 mm CR Closure	1 g cansiter
	1000's count	250 CC HDPE Container	53 mm CR Closure	2 g cansiter
	Bulk Pack (5000's)	5L Bucket with lid		(5 X 2) g cansiter
40 mg	90's count	40 CC HDPE Container	33 mm CR Closure	1 g cansiter
	1000's count	250 CC HDPE Container	53 mm CR Closure	2 g cansiter
	Bulk Pack (3000's)	5L Bucket with lid		(5 X 2) g cansiter
80 mg	100's count	250 CC HDPE Container	53 mm CR Closure	2 g cansiter
	500's count	750 CC HDPE Container	53 mm CR Closure	2 g cansiter
	Bulk Pack (1500's)	5L Bucket with lid		(5 X 2) g cansiter

2.5 Microbiological Attributes

An accelerated stability summary of the exhibit batch demonstrated that the drug product has low water activity and is not capable of supporting microbial growth. Routine microbiological testing of Generic Atorvastatin Calcium Tablets USP is unnecessary due to the low water activity of the product and controls on incoming raw materials.

2.6 Compatibility

This section is not applicable because the drug product is a solid oral dosage form and there are no reconstitution diluents.

2.7 Control Strategy

2.7.1 Control Strategy for Material Critical Material Attributes (CMAs)

The control strategy for Generic Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg are built upon the outcome of extensive product and process understanding studies. These studies investigated the material attributes and process parameters that were deemed high risk to the CQAs of the drug product during the initial risk assessment. In some cases, variables considered medium risk were also investigated. Through these systematic studies, the CMAs and CPPs were identified and the acceptable operating ranges were established. Thus, the control strategy is an integrated overview of how quality is assured based on current process and product knowledge. The control strategy may be further refined based on additional experience gained during the commercial lifecycle of the product. However, any post-approval changes should be reported to the agency in accordance with CFR 314.70 and should follow steps as outlined by guidances used for scale-up and post-approval changes. The control strategy of raw material attributes for commercial manufacture of generic Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg are proposed and provided in Table 123.

Table 123: Control Strategy for Critical Material Attributes (CMAs)

Factor	Critical Material Attributes	Range studied (lab scale)	Actual data for the exhibit batch (pilot scale)	Proposed range for commercial scale	Purpose of control
Drug Substance					
Atorvastatin Calcium Trihydrate USP	PSD	D_{10}: 1 µm D_{50}: 7 µm D_{90}: 20 µm	D_{10}: 1 µm D_{50}: 7 µm D_{90}: 20 µm	D_{10}: NMT 7 µm D_{50}: NMT 15 µm D_{90}: NMT 50 µm	To ensure uniform distribution of drug in the formulation. In-vitro dissolution, in-vivo performance and batch to batch consistency.
	Water determination	(4.6-4.73) % w/w	4.6 % w/w	Between (3.5 - 5.5) %.	To control the degradation and microbial growth of the drug product.
Excipient					
Precipitated Calcium Carbonate (Sturcal L)	Assay	99.3 %	98.6 %	(98.0-100.5) %	To ensure batch to batch consistency.
	Loss on drying	(0.2-0.6) %	0.6 %	NMT 2.0 %	
	Bulk density	0.83 g/mL	0.52 g/mL	NLT 0.40 g/mL	
Microcrystalline Cellulose (Vivapur 301)	PSD	1) Pass through >250 µm (60 mesh) : NMT 1 % 2) Pass through >75 µm (200 mesh): 23 % 3) Pass through >32 µm (469 mesh): 62 %	1) Pass through >250 µm (60 mesh) : 0 % 2) Pass through >75 µm (200 mesh): 22 % 3) Pass through >32 µm (450 mesh): 54 %	1) Pass through >250 µm (60 mesh) : NMT 1 % 2) Pass through >75 µm (200 mesh): NMT 30 % 3) Pass through >32 µm (450 mesh): NLT 55 %	To ensure batch to batch consistency for distribution and uniformity of drug substance as well to ensure consistent hardness at compression stage.
	pH	6.7- 6.91	6.7	5.0-7.5	
	LOD	(3.3 - 5.1) %	3.7 %	NMT 7.0 %	
	Bulk density	(0.37- 0.38) g/mL	0.42 g/mL	(0.35-0.46) g/mL	
	LOD	0.2 %	0.2 %	NMT 0.5 %	

Factor	**Critical Material Attributes**	**Range studied (lab scale)**	**Actual data for the exhibit batch (pilot scale)**	**Proposed range for commercial scale**	**Purpose of control**
Lactose Monohydrate (Pharmatose 200M)	Residue on Ignition	<0.1 %	0.1 %	NMT 0.1 %	To ensure batch to batch consistency for distribution and uniformity of drug substance as well to ensure consistent hardness at compression stage
	PSD	1. Pass on 45 µm Testing Sieve: 57 % 2. Pass on 150 µm Testing Sieve: 97 % 3. Pass on 250 µm Testing Sieve: 100 %	1. Pass on 45 µm Testing Sieve: 59 % 2. Pass on 150 µm Testing Sieve: 99 % 3. Pass on 250 µm Testing Sieve: 100 %	1. Pass on 45 µm Testing Sieve: (50-65) % 2. Pass on 150 µm Testing Sieve: (96-100) % 3. Pass on 250 µm Testing Sieve: (99-100) %	
Sodium Starch Glycolate Type A (Primojel®)	pH	6.6	6.7	5.5 – 7.5	To ensure batch to batch consistency in disintegration time.
	LOD	4.7 % w/w	5.7 % w/w	NMT 10.0 % w/w	
Polysorbate 80 (Kolliphor PS 80)	Saponification Value	52	52	45 – 55	To ensure batch-to-batch consistency in-vitro dissolution and in-vivo performance.
	Peroxide Value	(0 – 4)	0	NMT 10	
	Viscosity (25°C)	(407- 426) centistokes	474 centistokes	300–500 centistokes	
	Water determination	(2.51- 2.6) %	2.6 %	NMT 3.0 %	
Hydroxy Propyl Cellulose (Klucel EF Pharm)	LOD	(2.3-3.13) % w/w	2.8 % w/w	NMT 5.0 % w/w	To ensure batch-to-batch consistency.
	Viscosity (10% Viscosity, water, 25°C)	(122-470)cps	307 cps	Between (300-600) cps	
	pH	(6.0-6.3)	6.2	Between 5.0 and 8.0	
	Residue on Ignition	(0.2-0.4) %	0.4 %	NMT 0.8 % w/w	
Croscarmellose Sodium (Ac-Di-Sol® SD-711)	LOD	1.4%	2.9 %	NMT 10.0 %	To ensure batch to batch consistency in disintegration time.
	pH	6.5	6.5	5.0 - 7.0	

Factor	Critical Material Attributes	Range studied (lab scale)	Actual data for the exhibit batch (pilot scale)	Proposed range for commercial scale	Purpose of control
Magnesium Stearate (Veg)	Surface Area	(6.85- 11.2) m^2/g	6 m^2/g	Between 5 m2/g to 20 m2/g	To ensure sufficient lubrication and to reduce the risk of retarded dissolution.
	LOD	(3.39- 3.80) %	3.1 % w/w	NMT 6.0 % w/w	
Opadry II White (85F18422)	Ash Content (%, w/w)	(39.46-39.73) %	38.90%	(35.8 - 43.80) % w/w	To ensure batch-to-batch consistency.
Hypromellose 2910, 6 mPa.s (Pharmacoat 606)	Viscosity	(5.88-5.96) mPa.s	5.0 mPa.s	4.8 – 7.2 mPa.s	To ensure batch-to-batch consistency in coating solution viscosity
	Residue on Ignition	(0.59-0.60)%	0.5 %	NMT 1.5 %	
	pH	6.5-6.6	7.4	5.0 – 8.0	
	LOD	(1.4-1.6) %	2.9 %	NMT 5.0 %	
Opadry Clear (YS-1R-7006)	Ash Content (%, w/w)	0.14 %	0.80%	0.00%- 3.00%	To ensure batch-to-batch consistency.

2.7.2 Control Strategy for Process Parameters

Based on laboratory scale batches, formulation and process optimization summary results, process parameter at exhibit batches were established. Based on exhibit batches outcome a control strategy for process parameters has been proposed for commercial batch and summarized in Table 124.

Table 124: Control Strategy for Process Parameter

S/N	Process	Critical Process Parameter and/ in Process Control	Range studied (Lab scale)	Control for scale-up batch (Eng. Batch) Batch: 44.179 kg (common blend)	Control for the exhibit batch (pilot scale) Batch: 157.781 kg (common blend)	Proposed range for commercial scale	Purpose of control
1.	Co-sifting and Sifting	Equipment	Vibratory Sifter	Vibratory Sifter	Vibratory Sifter	Vibratory Sifter	To separate and break up lumps in dry ingredients
		Mesh Size	# 20	# 20	# 20	# 20	
2.	Pre Mixing	Equipment	Bin Blender	Bin Blender	Bin Blender	Bin Blender	-

S/N	Process	Critical Process Parameter and/ in Process Control	Range studied (Lab scale)	Control for scale-up batch (Eng. Batch) Batch: 44.179 kg (common blend)	Control for the exhibit batch (pilot scale) Batch: 157.781 kg (common blend)	Proposed range for commercial scale	Purpose of control
		Mixing: No. of Revolution	100	100	100	100	To ensure batch to batch consistency in mixing
3.	Top Spray Granulation	Fluid Bed Processor (Volume)	(4-40) L	368L	368L	1800L	-
		Inlet air temperature	65 ± 15ºC	65 ± 10ºC	60 ± 10ºC	60 ± 10ºC	To ensure batch to batch consistency of Particle Size Distribution and Density in order to warrant Uniform Flow property and compressibility
		Product bed temperature	40 ± 10ºC	40 ± 10ºC	40 ± 10ºC	40 ± 10ºC	
		Drying time	(15-30) Min	18 Min	(25-60) Min	(25-60) Min	
		Loss on drying at 105°C	NMT 2.5%	NMT 2.5%	NMT 2.5%	NMT 2.5%	
4.	Size Reduction	Vibratory sifter	N/A	# 20 mesh	# 20 mesh	# 20 mesh	To separate and break up lumps of granules
		Co-mill	N/A	1.2 mm	1.2 mm	1.2 mm	
5.	Blending and Lubrication	Bin Blender (Volume)	(5-50) L	400 L	1500 L	1500 L	-
		Mesh Size	# 40	# 40	# 40	# 40	To ensure batch to batch consistency in blend uniformity and content uniformity
		Pre-lubrication: No. of Revolution	60-100 (optimized range)	100	100	100	
		Lubrication: No. of Revolution	30-50 (optimized range)	50	50	50	
6.	Compression	Group weight of **10 mg**	2.875 g ± 5.0 % (2.731–3.019) g	2.875 g ± 5.0 % (2.731–3.019) g	2.875 g ± 5.0 % (2.731–3.019) g	2.875 g ± 5.0 % (2.731–3.019) g	To meet intermediate

S/N	Process	Critical Process Parameter and/ in Process Control		Range studied (Lab scale)	Control for scale-up batch (Eng. Batch) Batch: 44.179 kg (common blend)	Control for the exhibit batch (pilot scale) Batch: 157.781 kg (common blend)	Proposed range for commercial scale	Purpose of control
		20 Tablets	**20 mg**	5.750 g ± 5.0 % (5.463–6.038) g	5.750 g ± 5.0 % (5.463–6.038) g	5.750 g ± 5.0 % (5.463–6.038) g	5.750 g ± 5.0 % (5.463–6.038) g	CQAs of drug product
			40 mg	11.500 g ± 3.0 % (11.155–11.845) g	11.500 g ± 3.0 % (11.155–11.845) g	11.500 g ± 3.0 % (11.155–11.845) g	11.500 g ± 3.0 % (11.155–11.845) g	
			80 mg	23.00 g ± 3.0 % (22.310–23.690) g	23.00 g ± 3.0 % (22.310–23.690) g	23.00 g ± 3.0 % (22.310–23.690) g	23.00 g ± 3.0 % (22.310–23.690) g	
		Uniformity of weight	**10 mg**	143.750 mg ± 7.5 % (132.969–154.531) mg	143.750 mg ± 7.5 % (132.969–154.531) mg	143.750 mg ± 5.0 % (136.563 mg – 150.938 mg)	143.750 mg ± 5.0 % (136.563 mg – 150.938 mg)	
			20 mg	287.500 mg ± 7.5 % (265.938–309.063) mg	287.500 mg ± 7.5 % (265.938–309.063) mg	287.500 mg ± 5.0 % (273.125 mg – 301.875 mg)	287.500 mg ± 5.0 % (273.125 mg – 301.875 mg)	
			40 mg	575.000 mg ± 5.00 % (546.250–603.750) mg	575.000 mg ± 5.00 % (546.250–603.750) mg	575.000 mg ± 5.00 % (546.250–603.750) mg	575.000 mg ± 5.00 % (546.250–603.750) mg	
			80 mg	1150.000 mg ± 5.00 % (1092.500–1207.500) mg	1150.000 mg ± 5.00 % (1092.500–1207.500) mg	1150.000 mg ± 5.00 % (1092.500–1207.500) mg	1150.000 mg ± 5.00 % (1092.500–1207.500) mg	
		Hardness	**10 mg**	(6-14) kp Target- 10.0 kp	(6-14) kp Target- 10.0 kp	(6-14) kp Target- 10.0 kp	(6-14) kp Target- 10.0 kp	

S/N	**Process**	**Critical Process Parameter and/ in Process Control**		**Range studied (Lab scale)**	**Control for scale-up batch (Eng. Batch) Batch: 44.179 kg (common blend)**	**Control for the exhibit batch (pilot scale) Batch: 157.781 kg (common blend)**	**Proposed range for commercial scale**	**Purpose of control**
			20 mg	(9-17) kp Target- 13.0 kp	(9-17) kp Target- 13.0 kp	(9-17) kp Target- 13.0 kp	(9-17) kp Target- 13.0 kp	
			40 mg	(13-21) kp Target- 17.0 kp	(13-21) kp Target- 17.0 kp	(12-20) kp Target- 16.0 kp	(12-20) kp Target- 16.0 kp	
			80 mg	(18-26) kp Target- 22.0 kp	(18-26) kp Target- 22.0 kp	(16-26) kp Target- 21.0 kp	(16-26) kp Target- 21.0 kp	
		Thickness	**10 mg**	3.30 mm ± 0.40 (2.90-3.70) mm	3.30 mm ± 0.40 (2.90-3.70) mm	3.30 mm ± 0.40 (2.90-3.70) mm	3.30 mm ± 0.40 (2.90-3.70) mm	
			20 mg	4.50 mm ± 0.40 mm (4.10 to 4.90 mm)	4.50 mm ± 0.40 mm (4.10 to 4.90 mm)	4.50 mm ± 0.40 mm (4.10 to 4.90 mm)	4.50 mm ± 0.40 mm (4.10 to 4.90 mm)	
			40 mg	5.40 mm ± 0.40 (5.00-5.80) mm	5.40 mm ± 0.40 (5.00-5.80) mm	5.40 mm ± 0.40 (5.00-5.80) mm	5.40 mm ± 0.40 (5.00-5.80) mm	
			80 mg	7.10 mm ± 0.40 (6.70-7.50) mm	7.10 mm ± 0.40 (6.70-7.50) mm	7.10 mm ± 0.40 (6.70-7.50) mm	7.10 mm ± 0.40 (6.70-7.50) mm	
		Disintegration Time **(10 mg, 20 mg, 40 mg and 80 mg)**		NMT 15 minutes determined on 6 tablets (without disc)	NMT 15 minutes determined on 6 tablets (without disc)	NMT 15 minutes determined on 6 tablets (without disc)	NMT 15 minutes determined on 6 tablets (without disc)	
		Friability **(10 mg, 20 mg, 40 mg and 80 mg)**		NMT 1.0% w/w on NLT 6.50 g tablets.	NMT 1.0% w/w on NLT 6.50 g tablets.	NMT 1.0% w/w on NLT 6.50 g tablets.	NMT 1.0% w/w on NLT 6.50 g tablets.	

S/N	**Process**	**Critical Process Parameter and/ in Process Control**		**Range studied (Lab scale)**	**Control for scale-up batch (Eng. Batch) Batch: 44.179 kg (common blend)**	**Control for the exhibit batch (pilot scale) Batch: 157.781 kg (common blend)**	**Proposed range for commercial scale**	**Purpose of control**
		Dimension of Tablet	**10 mg**	9.80 × 5.10 mm, oval shaped	9.80 × 5.10 mm, oval shaped	9.80 × 5.10 mm, oval shaped	9.80 × 5.10 mm, oval shaped	
			20 mg	12.30 × 6.40 mm, oval shaped	12.30 × 6.40 mm, oval shaped	12.30 × 6.40 mm, oval shaped	12.30 × 6.40 mm, oval shaped	
			40 mg	15.50 × 8.15 mm, oval shaped	15.50 × 8.15 mm, oval shaped	15.50 × 8.15 mm, oval shaped	15.50 × 8.15 mm, oval shaped	
			80 mg	19.30 × 10.35 mm, oval shaped	19.30 × 10.35 mm, oval shaped	19.30 × 10.35 mm, oval shaped	19.30 × 10.35 mm, oval shaped	
7.	Coating	Atomizing Air Pressure		(1.0 – 2.5) Bar	(2.0 – 4.0) Bar	(1.0 – 4.0) Bar	(2.0 – 3.0) Bar	To meet drug product CQAs as well as physical attributes
		Inlet Temperature		60±10ºC	60±10ºC	60±10ºC	60±10ºC	
		Pan Rotation Speed		(4-15) RPM	(1.5-15) RPM	(1.5-15) RPM	(1-4) RPM	
		Weight gain		3.0 % w/w to 5.0 % w/w	4.0 % w/w (3.5 % w/w to 5.0 % w/w)	4.0 % w/w (3.5 % w/w to 5.0 % w/w)	4.0 % w/w (3.5 % w/w to 5.0 % w/w)	
		Peristaltic pump RPM		(5-20) RPM	(5-30) RPM	(5-30) RPM	(5-30) RPM	
		Spray rate		N/A	(50±20) g/min/gun	(50±20) g/min/gun	(200±50) g/min/gun.	
		Nozzle size		(0.8-1.2) mm	1.0 mm	1.0 mm	1.0 mm	
		Spray nozzles should be perpendicular to rolling bed of tablets		Perpendicular	Perpendicular	Perpendicular	Perpendicular	
		Spray nozzles distance from bed		(15-25) cm	(10-25) cm	(10-25) cm	(15-25) cm	

S/N	**Process**	**Critical Process Parameter and/ in Process Control**	**Range studied (Lab scale)**	**Control for scale-up batch (Eng. Batch) Batch: 44.179 kg (common blend)**	**Control for the exhibit batch (pilot scale) Batch: 157.781 kg (common blend)**	**Proposed range for commercial scale**	**Purpose of control**
		Overages of coating solution to compensate the process loss	(10-20) %	20 %	20 %	20 %	
		Sieving of coating suspension	ASTM # 80 mesh	ASTM # 80 mesh	ASTM # 80 mesh	ASTM # 80 mesh	

2.8 Overall Conclusion of Product Development

In accordance with FDA's pre-defined guidance (Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms, April 2012), AHL's development strategy and the generated data on development and exhibit batches we consider the process to be robust and reproducible for commercialization. The risk assessment process has been thoroughly evaluated and the impact has been analyzed to develop an optimized formula of Atorvastatin Calcium Tablets USP. The summary results of the optimized formulation met in-process, release and stability acceptance criteria.

2.9 Product Lifecycle Management and Continual Improvement

Upon approval, the manufacturing process for Atorvastatin Calcium Tablets USP, will be validated using the lifecycle approach that employs risk-based decision making throughout the drug product lifecycle as defined in the FDA process validation guidance.

Throughout the product lifecycle, the performance of the manufacturing process will be monitored to ensure that the drug product meets all acceptance criteria as anticipated to deliver the product with desired quality attributes. Process stability and process capability will be measured and evaluated during validation campaign. If any unexpected process variability is detected, appropriate measure will be taken to correct, anticipate, and prevent future problems so that the process remains in control acceptance criteria. The additional knowledge gained during routine post marketing manufacturing will be utilized for adjustment of process parameters as part of the continual improvement of the drug product. As a commitment, the regulatory agency will be notified in accordance with CFR 314.70 regarding each change in each condition beyond the variability already provided throughout the shelf life of this application.

Profile of ABM Mahfuz ul Alam, Ph.D.

A.B.M. Mahfuz Ul Alam is a Bangladeshi pharmaceutical scientist and academician. He is currently the Director of Quality Operations at ACI Healthcare Limited, a multinational pharmaceutical company headquartered in Dhaka, Bangladesh. He is also an Adjunct Faculty Member at the Independent University, Bangladesh. Dr. Alam received his PhD in Analytical Method Development for Pharmaceutical Products Using Quality By Design (QbD) Concept from the University of Dhaka in 2019. He has over 24 years of experience in the pharmaceutical industry, working in various capacities in quality management, project management, validation, research and development, regulatory affairs, and audits. He has extensive experience in designing and implementing QA and QC processes and Quality Management Systems, and in developing and submitting new products in the EU, US, and other markets. He has also led teams for successful inspections of the US FDA, EU GMP, ANVISA, and MCC. He is a valuable asset to ACI Healthcare Limited and the Independent University, Bangladesh.